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STUDIES ON CORPUS LUTEUM FUNCTION

I. THE URINARY EXCRETION OF SODIUM PREGNANEDIOL GLUCURONIDATE IN THE HUMAN MENSTRUAL CYCLE.

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Our understanding of the mechanism and physiology of the menstrual cycle has been greatly clarified in recent years, from the chemical aspect by the preparation and use of crystalline ovarian hormones and from the anatomical aspect by the taking of repeated endometrial biopsies. Much work has been done on the quantitative determination in urine and blood of the estrogens and gonadotropic hormones. Up to within the last year, however, the assay of the corpus luteum hormone progesterone, in body tissues and fluids, had failed to throw any light upon the relative amounts of this hormone produced in the body. Loewe and Voss (1) found that 20 litres of urine collected during pregnancy and the latter half of the menstrual cycle contained only 1 Clauberg Rb.U. of progesterone. Clauberg and co-workers (2) and Pratt (3) respectively reported that it required extracts of human corpora lutea corresponding to 55 to 60 gm. of tissue to give a positive reaction for this hormone. Bloch (4) was unable to detect progesterone in 500 cc. of blood from pregnant women.

The isolation of sodium pregnanediol glucuronidate from human pregnancy urine by Venning and Browne (5) with the evidence (6, 7, 8) that the excretion of this compound both during pregnancy and in the menstrual cycle is associated with the production of the corpus luteum hormone progesterone, is no doubt, the explanation for the previous failures to detect this hormone in any quantity. As experimental proof of the relationship between these two compounds in the body, progesterone (19 and 28 mg.) was injected intramuscularly into 2 patients in whom there was a reasonable certainty that no corpus luteum was present at the time of the injection; 46 per cent and 40 per cent, respectively, of the injected progesterone was recovered in the urine in the form of sodium pregnanediol glucuronidate. In another case, that of an oöphorectomized woman with the uterus intact, 30 mg. of progesterone was injected and 12 per cent was recovered in the urine in the

form of the above compound. The compound isolated from these experiments and from the luteal phase of the menstrual cycle appears to be identical with the compound excreted throughout pregnancy. The measurement of sodium pregnanediol glucuronidate in the urine should therefore offer a means of determining the duration and functional activity of the corpus luteum. A preliminary account of the findings of the excretion of this compound in the menstrual cycle and throughout pregnancy has already been reported by the above authors (6) and by Venning, Henry and Browne (7) and Browne, Henry and Venning (8).

Briefly, the present conception of the events that take place during the ovulatory type of menstrual cycle is as follows. After menstruation the uterine mucosa is regenerated and, under the influence of the estrogens, is gradually built up during the proliferative stage. During this period or follicular phase, there is a ripening of the graafian follicle in the ovary. About the midcycle following an added stimulus (qualitative or quantitative) from the pituitary, the mature follicle ruptures and discharges its ovum. Immediately following ovulation a corpus luteum is formed which produces progesterone and also probably continues to produce estrogens. This latter part of the menstrual cycle is called the luteal phase. Due to the action of progesterone, the already proliferated endometrium is transformed into the secretory or progestational stage in preparation for the implantation of the fertilized ovum. If the ovum is not fertilized the corpus luteum degenerates and this is followed by a breakdown and shedding of the endometrium which is accompanied by the menstrual flow.

The object of this present investigation is to study, by means of the urinary excretion of sodium pregnanediol glucuronidate, the variations that occur in the life and functional activity of the corpus luteum during the menstrual cycle in a series of cases of apparently healthy cyclic women. The sodium pregnanediol glucuronidate was determined by the gravimetric method described by one of us (9), which consists in extracting the urine with butyl alcohol and subsequently precipitating the sodium pregnanediol glucuronidate by means of acetone. The precipitate is weighed as sodium pregnanediol glucuronidate and the amount of free pregnanediol in this compound is calculated by means of a factor. Pregnanediol is a reduction product of progesterone and, as the molecular weights of these two substances are almost identical (316 and 320 respectively), the amount of pregnanediol excreted may be conveniently compared to an equivalent weight of progesterone, from which it is thought to be derived. Complete 24-hour specimens of urine were collected in all the cases from about the 10th day of the cycle onwards up to the time of the next bleeding, and were analyzed for the presence of sodium pregnanediol glucuronidate. The results in the tables are expressed in terms of milligrams of pregnanediol excreted per 24 hours. The urine was also assayed for gonadotropic substance. The method employed was the tannic acid precipitation method of Levin and Tyndale (10). A full squamous vaginal smear using 21-day-old female rats was taken as a positive result. Kurzrok, Kirkman and Creelman (11) have shown that the excretion of gonadotropic substance frequently immediately precedes ovulation and it was hoped by this means to detect the occurrence of ovulation in the various menstrual cycles. In 2 of the cases the time of ovulation was approximated by the clinical signs generally assumed to be associated with this phenomenon: intermenstrual

bleeding and intermenstrual pain. One view of the causation of the 'Mittelschmerz' or intermenstrual pain is that it is due to the distention of the follicle just prior to rupture and Hartman (12) has reported that 75 per cent of the Macacus rhesus monkeys have intermenstrual bleeding and that it is associated with ovulation.

A series of charts (fig. 1) has been drawn for the various cases depicting graphically the menstrual cycle with the excretion of gonadotropic substance and pregnanediol. The horizontal lines represent the length of the menstrual cycles; the oblique lines at the beginning of the cycle, the days of menstrual bleeding The shaded part is the excretion of pregnanediol in mg. per day. When gonadotropic substance was present it is marked below the horizontal line by the letter A. The first day on which 24-hour urine specimens were collected is indicated by X. Intermenstrual bleeding or intermenstrual pain is denoted by an arrow above the horizontal line.

CASE HISTORIES

Case. 1. The patient was a married woman aged 42 years. Her menses began at 12 years. The length of the cycles was from 28 to 30 days. The flow was moderate, without pain, lasting 4 days.

The 3 horizontal lines on the chart (fig. 1, *case 1*) represent the length of 3 consecutive cycles. In the third cycle of 30 days duration, collections of urine were made from the 10th day onwards. No gonadotropic substance was detected at any time in this cycle. Pregnanediol first appeared on the 19th day and was excreted continuously for 10 days. A total amount of 42.0 mg. of pregnanediol was obtained, the maximum excretion being 6 mg. per day. Two days following the disappearance of this compound from the urine bleeding occurred.

Case 2. The patient was 22 years of age, single, and had a normal menstrual history. The menses began at 12 years, and were of 25 to 29-day type. The flow was moderate, lasting 4 to 5 days. The cycles were characterized by a sharp pain occurring at the mid-cycle for about 2 to 6 hours, usually in the right lower quadrant, but occasionally in the left, and always more severe on the right side. The day on which the intermenstrual pain occurred was recorded for the last 6 cycles.

Length of Cycle	Intermenstrual Pain	Side	Length of Luteal Phase Calculated from Day of Intermenstrual Pain
25 days	11th day	right	14 days
28 "	14th "	"	14 "
29 "	14th "	left	15 "
27 "	13th "	right	14 "
26 "	none	—	—
28 "	14th "	left	14 "

The length of the cycle studied was 25 days and collections of urine were begun on the 8th day. Gonadotropic substance was excreted both on the 10th day and on the morning of the 11th day, the intermenstrual pain occurring on the afternoon of the 11th day. Pregnanediol was excreted from the 13th to the 22nd day. The onset of the next period followed 2 days after the disappearance of pregnanediol from the urine. The total amount of pregnanediol excreted was 51.2 mg., the maximum excretion per day being 6.4 mg. In the next cycle of 28 days' duration the intermenstrual pain occurred on the 14th day. No assays were carried out in this cycle.

Case 3. The patient was a married woman, aged 35 years. Menses began at 11 years. The length of the cycles varied from 24 to 29 days; the flow was profuse, lasting 5 days. The early menstrual history was characterized by considerable amount of bleeding throughout the cycle, particularly after muscular exercise. The inter-

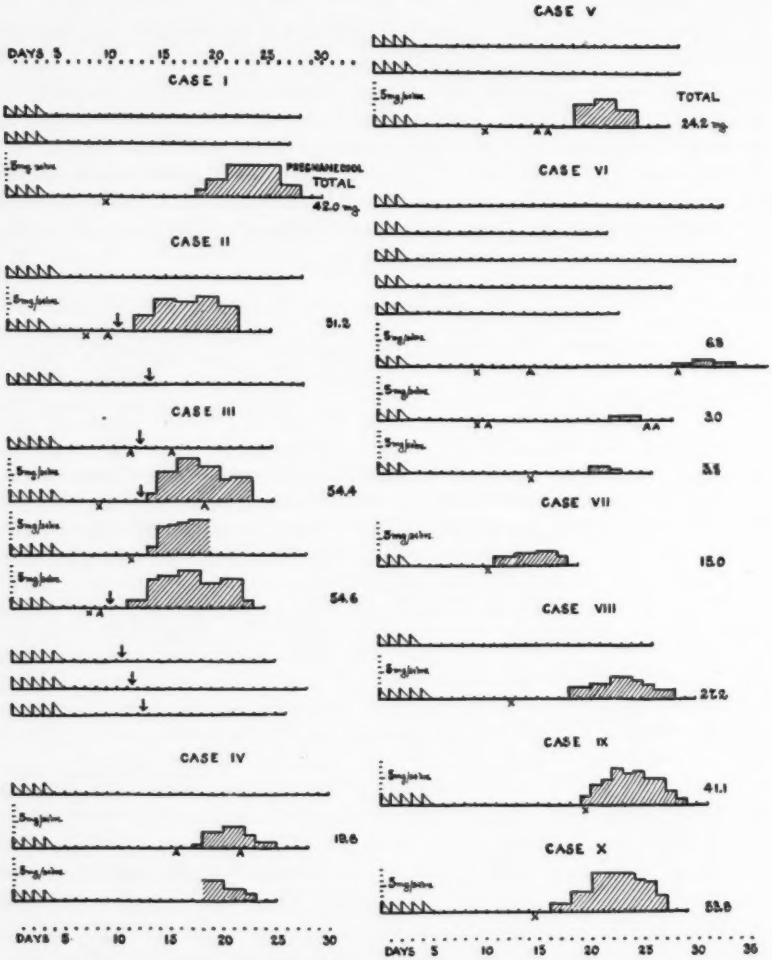

Fig. 1. Excretion of pregnanediol in the menstrual cycle.

menstrual bleeding or spotting is now confined to one day about the midcycle. The length of the first cycle studied was 25 days. Only morning specimens were collected in this cycle for the determination of gonadotropic substance. A positive response was obtained on the 12th day, 24 hours before the appearance of the intermenstrual bleeding and again on the 16th day. In the next cycle, complete 24-hour collections were begun on the 9th day. Intermenstrual bleeding occurred on the 13th day and pregnanediol appeared in the urine on the following day. A total amount of

54.4 mg. was excreted over 10 days, the maximum amount obtained per day being 8.1 mg. Menstrual bleeding occurred 2 days following its disappearance from the urine. In the third cycle intermenstrual bleeding occurred on the 12th day, pregnanediol was excreted on the 14th day. Unfortunately it was not possible to complete the investigations on this particular cycle. In the fourth cycle of 24 days' duration, collections were begun on the 8th day, gonadotropic substance was present on the 9th day and intermenstrual bleeding occurred on the 10th day. Pregnanediol appeared on the 12th day, a total amount of 54.6 mg. being excreted over a period of 12 days. The maximum excretion per day was 7.0 mg. The next period began 1 day following the cessation of excretion of this compound. In the last 3 cycles, of 25, 28 and 26 days respectively, the intermenstrual bleeding occurred on the 11th, 12th and 13th day. In this case a record of the time of intermenstrual bleeding has been kept for the last 2 years. It is of interest to note the variations occurring both in the length of the cycle and in the time of intermenstrual bleeding.

Length of Cycle	Intermenstrual Bleeding	Length of Luteal Phase Calculated from Day of Intermenstrual Bleeding
27 days	14th day	13 days
29 "	15th "	14 "
27 "	11th "	16 "
22 "	11th "	11 "
27 "	12th "	15 "
29 "	13th "	16 "
25 "	12th "	13 "
25 "	13th "	12 "
25 "	11th "	14 "
27 "	12th "	15 "
25 "	13th "	12 "
28 "	12th "	16 "
24 "	10th "	14 "
25 "	11th "	14 "
28 "	12th "	16 "
26 "	13th "	13 "
24 "	10th "	14 "
25 "	12th "	13 "
27 "	14th "	13 "
29 "	15th "	14 "
22 "	8th "	14 "
24 "	9th "	15 "

The length of the cycles over this period varied from 22 to 29 days. Intermenstrual bleeding occurred once on the 8th day, once on the 9th day, twice on the 10th, 4 times on the 11th, 6 times on the 12th, 4 times on the 13th, twice on the 14th and twice on the 15th.

Case 4. Fig. 2. The patient was a single woman, 24 years of age. Menses began at 12 years. The cycles varied in the last 9 months in the following manner: 28-30-28-25-28-41-30-27-32 days. The menstrual flow lasted from 3 to 4 days, was moderate, but was usually accompanied by pain.

The length of the first cycle studied was 28 days. Urine specimens were collected from the 10th day onwards. Gonadotropic substance was excreted on the 16th day and pregnanediol appeared in the urine on the 18th day. A total amount of 19.6 mg. of pregnanediol was excreted in 8 days. The maximum excretion was 4.0 mg. per day. Three days later bleeding occurred. A second excretion of gonadotropic substance was detected on the 22nd day. In the next cycle collections of urine were not begun until the 19th day and it was found that pregnanediol was already being excreted at that time. Two days following its disappearance, bleeding occurred. The maximum excretion per day was 4.5 mg.

Case 5. The patient was a married woman aged 38 years. She had a normal menstrual history. Menses began at 15 years. The very regular cycles were of 28 to 29 days' duration. The flow was moderate and lasted for 4 days. Collections of urine were begun on the 10th day. The duration of the cycle was 28 days, gonadotropic substance was excreted on the 16th and 17th days and pregnanediol on the 20th day. A total amount of 24.2 mg. of pregnanediol was obtained over 6 days, the maximum excretion per day being 5 mg. Three days following its disappearance from the urine bleeding began. This patient had a history of sterility for many years.

Case 6. The patient was a single woman, aged 23 years. Menses began at 14 years, were usually regular in length, but over the period followed several irregular cycles occurred. The flow was scanty, lasting 3 days, without pain. The length of consecutive cycles during the last year varied as follows: 32-22-34-28-23-27-27-28-

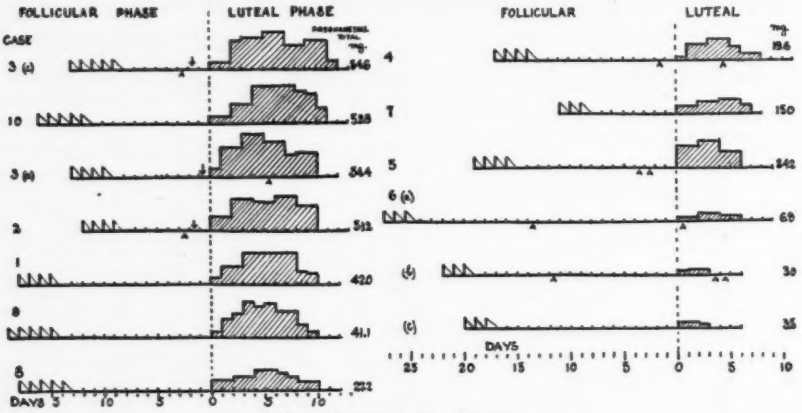

Fig. 2. Summary chart of the cases.

28-26-29-29-28 days. Three complete cycles were investigated. The length of the first cycle was 37 days and collections were begun on the 10th day. Gonadotropic substance appeared in the urine on the 15th, 29th and 30th days, pregnanediol was not excreted until the 29th day. An extremely small amount, 6.8 mg., was excreted over a period of 6 days, the maximum excretion per day being 1.5 mg. Three days after its disappearance from the urine, bleeding occurred. The length of the second cycle was 28 days. Gonadotropic substance appeared in the urine on the 11th, 26th and 27th days. Pregnanediol was not excreted until the 23rd day. A total amount of 3.0 mg. was excreted over 3 days. Again bleeding occurred 3 days following the disappearance of pregnanediol from the urine. The length of the third cycle was 26 days. Collections were not begun until the 15th day. No gonadotropic substance was detected; 3.5 mg. of pregnanediol were excreted for 3 days at the end of the cycle and bleeding occurred 3 days following its disappearance. The amount excreted per day in the 3 cycles varied from 1 to 1.5 mg.

Case 7. A married woman, 45 years of age, had a normal menstrual history. The cycles were usually 28 to 29 days in length but the only one examined was very short, only 19 days. Pregnanediol appeared in the urine on the 12th day and a total of 15.0 mg. was excreted in 7 days, the maximum excretion per day being 2.4 mg. Bleeding occurred on the day following the disappearance of this compound from the urine. No gonadotropic substance was detected in this cycle.

Case 8. Fig. 4. The patient was a single woman 30 years of age. Menses began at 13 years. The cycles were usually 26 to 28 days in length with moderate flow lasting 4 to 5 days without pain. The length of the cycle examined was 31 days. No gonadotropic substance was detected. Pregnanediol appeared in the urine on the 19th day and was excreted for 10 days (total 27.2 mg.), the maximum excretion being 4.0 mg. per day. Two days following its disappearance from the urine bleeding occurred.

Case 9. The patient was 30 years of age, single. Menses began at 12 years. The cycles were irregular. The flow lasted from 4 to 6 days and severe pain occurred at the onset of each period. The length of the cycle studied was 31 days. Pregnanediol appeared in the urine on the 20th day; a total amount of 41.1 mg. was excreted over a period of 10 days, the maximum excretion per day being 6.8 mg. Two days following its disappearance from the urine bleeding occurred.

Case 10. The subject was 30 years old, married. She had a normal menstrual history. The cycles were regular. The flow was profuse, lasting from 4 to 6 days. Headaches usually accompanied the onset of the period. The length of the cycle studied was 29 days. Pregnanediol appeared on the 17th day, a total amount of 53.8 mg. being excreted over a period of 11 days. The maximum excretion was 7.2 mg. per day. Twenty-four hours following its disappearance from the urine bleeding occurred. No gonadotropic assays were carried out on this case.

DISCUSSION

A summary chart of the various cases has been drawn in figure 2. They have been arranged in descending order with regard to the length of the luteal phase and the division of the cycle into follicular and luteal phase has been made according to the time of appearance of pregnanediol in the urine.

The following deductions may be drawn from a study of these cases. *1.* This combined form of pregnanediol is not excreted at any time in the follicular phase but only in the luteal phase of the menstrual cycle. The excretion coincides with the time in which there is supposed to be a corpus luteum in the ovary and this fact alone suggests at once a relationship between the formation of a corpus luteum in the ovary and the appearance of pregnanediol in the urine. Also it is not excreted spasmodically but once it appears in the urine, its excretion is continuous. The amount is low at first, reaching a maximum about one-third of the way through the period of excretion and then falling off at the end. Sometimes the disappearance of the compound is quite abrupt. The excretion period varies from 3 to 12 days. Of the 10 cases followed, 6 excreted pregnanediol over a period of 10 to 12 days, 3 from 6 to 8 days and in *case* 6 the excretion was only for 3 days in 2 cycles and 6 days in the third.

2. It is well recognized that, when careful records are kept by the calendar, of the length of the menstrual cycle, a regular 28 day cycle is the exception rather than the usual finding. In only 1 of the 10 cases studied was there a record of definitely regular cycles, although when first questioned, all stated that they were regular. There is usually a spread of at least 4 days in the average cycle with a tendency to be more irregular in the summer than in the winter time. When the cycle is divided into the two phases by means of the above excretion of pregnanediol it would seem that the irregularities that occur in the length of the cycle in any one case can be accounted for to a great

extent in the follicular phase, although there is also a certain amount of variation in the luteal phase. The time taken for the follicle to ripen and rupture would appear to be more variable than the span of activity of the corpus luteum. When the ovulation is shifted, then the length of the period is shifted accordingly. In *case 2,* this is shown very clearly in the first two cycles. When the intermenstrual pain occurs on the 11th day the cycle is 25 days, in the next period the pain does not occur until the 14th day and in consequence the period is lengthened by 3 days. *Case 3* and *case 4* also show similar variations. However according to Schröder (16), the length of the follicular phase is less of a variable than the life span of the corpus luteum. He states that in lengthened irregular cycles there is apt to be a period of rest, the true follicular phase not beginning for some time after menstruation and that in these cases there is actually a shortening of the luteal phase. This theory would help to account for some of the irregularities that occurred in the cycles in *case 6.* The luteal phase in *case 3* as timed by the occurrence of intermenstrual bleeding varied from 11 to 16 days over 22 periods, whereas the follicular phase varied from 8 to 15 days. In *case 2* over a period of 5 cycles there was only a slight variation of a day in the length of the luteal phase.

3. In *cases 2* and *3* where the ovulation was approximated by means of the intermenstrual pain and bleeding, pregnanediol appeared in the urine usually within 48 hours. In one cycle however it was detected as early as 24 hours after ovulation. This difference in the time taken for pregnanediol to appear in the urine can no doubt be partly accounted for by the manner of collection as the 24-hour specimens were timed from 8 a.m. to 8 a.m. regardless of the time at which the pain or bleeding occurred. The work of Kurzrok, Kirkman and Creelman (11) suggests that the excretion of gonadotropic substance at the midcycle usually precedes ovulation by 24 hours. It was not always possible to detect this substance in the various cycles and frequently it was positive on more than just the one day preceding ovulation. In *cases 2, 3, 4,* and *5,* gonadotropic substance was detected in the urine at a time that would closely agree with the day of ovulation as approximated by the subsequent excretion of pregnanediol. In *cases 2* and *3* where ovulation was thought to occur at the time of intermenstrual pain or bleeding, gonadotropic substance was present in some of the cycles on the day preceding this phenomenon. The failure to detect gonadotropic substance in many of the cases may be due, partly to the method of assay and possibly to the fact that it may only be excreted over a short period. When 24-hour specimens are collected, the concentration of gonadotropic substance may be so lowered by dilution with the total volume as to be undetectable, for in one case it was found that when the various fractions were assayed separately throughout the day, gonadotropic substance could only be detected in one 4-hour specimen.

4. Due to the lack of endometrial biopsies in the cases studied, it has not been possible to correlate the changes occurring in the endometrium with the amount of pregnanediol excreted. The total amount varied from 3.0 mg. to 54.6 mg. Five of the cases excreted from 41 to 54.0 mg., 4 from 15 to 27 mg.

and *case 6* from 3 to 6 mg. There apparently can exist all stages of activity of the corpus luteum and no doubt there may be considerable variation even in the same person if sufficient cycles were followed. The above results suggest the possibility that 40 to 55 mg. of pregnanediol may be an average value but it is impossible at this stage with so few cases studied to judge what might constitute an adequate production of progesterone. Kaufmann (13) and Clauberg (14) found that in oöphorectomized women it required from 35 to 90 Rb.U. of luteo hormone (after a pre-treatment with progynon benzoate) to produce a progravid endometrium. These quantities agree with the highest values found for the excretion of pregnanediol in the above cases. In *case 5* and 7 where there is not only a lowering in the total amount of pregnanediol excreted but also a shortened luteal phase, there is a history of functional sterility and in several cases of sterility which are now being investigated and will be reported later in detail, an excretion of pregnanediol similar to *case 6* is found. The presence of these very small amounts of pregnanediol at the end of the cycle is of particular interest. Robert Meyer (15) has described a condition that can occur in the corpus luteum and which would probably cause a decrease in the production of progesterone. Occasionally there is a breaking off of the granulosa layer before luteinization occurs, this loss influences the activity of the corpus luteum and may cause premature degeneration to set in. Partial luteinization can also occur in atretic follicles. If after death of the egg the granulosa is not shed off in toto, a small portion may remain alive and become luteinized. Schröder (16) states that this is only possible in the presence of a corpus luteum, but now that it has been established that the process of luteinization is under the influence of the pituitary it is possible that partial luteinization of atretic follicles can occur independently of a corpus luteum. Stieve (17) has reported the finding of partial luteinization in an unruptured follicle where the ovum was still alive. These findings however appear to be rare but they are suggestive and the possibility of their occurrence should not be overlooked.

5. Regardless of the variation in the length of the cycle or in the luteal phase itself, the timing of the next menstrual flow appears to be closely correlated with the cessation of the excretion of pregnanediol. Bleeding always occurs within 1 to 3 days following the disappearance of this compound. These observations agree with the investigations carried out on the excision of the corpus luteum. Pratt (18) and many others have demonstrated that removal of the corpus luteum in monkeys results in menstruation in 2 to 6 days. Corner and Allen (19) report that bleeding occurred in monkeys 2 to 4 days after discontinuance of treatment with crystalline progesterone. Wiesbader, Engle and Smith (20) find that in the human being after the ablation of the corpus luteum, massive doses of estrin could not prevent bleeding, but that adequate doses of progesterone would inhibit it. Bleeding in these cases occurs 2 to 4 days after cessation of the progesterone treatment. Several theories have been put forward to explain the cause for the onset of bleeding, among them Allen's estrin deprivation theory of menstruation. It is now well recognized that

bleeding can occur both in the monkey and in the human being without ovulation or the formation of a corpus luteum. No doubt in this particular type of cycle a sudden drop in the estrin level would help to explain the onset of bleeding. However in the ovulatory type of menstrual cycle it has been shown by careful study of numerous histological sections of the ovary that the degeneration of the corpus luteum as indicated by the breakdown of the cells and the infiltration of lipids occurs at the onset of menstruation. A coincident lowering in the production of progesterone has been considered to be a factor in the initiation of bleeding. Bachmann (21) reports that in one of his cases degeneration had already set in shortly before menstruation. Even in *case 6* where there is considerable variation in the length of the cycle and where the luteal phase is extremely short (only 3 mg. of pregnanediol being excreted over 3 days in 2 of the cycles) the onset of the next period is correlated with the disappearance of this compound from the urine.

There are several factors which may influence the excretion of sodium pregnanediol glucuronidate. The efficiency of the renal excretion as well as the efficiency of the mechanism of the conjugation of pregnanediol with glucuronic acid may be of importance, as free pregnanediol itself is only found in very small amounts in urine. It is also possible that the state of the endometrium may influence the conversion of progesterone to pregnanediol. Recent work done in our laboratories suggests that the presence of the uterus or an endometrium is a necessary factor, for, after injections of progesterone into hysterectomized women, sodium pregnanediol glucuronidate failed to appear in the urine.

SUMMARY

The quantitative excretion of sodium pregnanediol glucuronidate in the human menstrual cycle in 10 cases is reported. This compound is considered to be an excretion product of progesterone. It is only excreted in the luteal phase of the menstrual cycle and appears in the urine within 24 to 48 hours after ovulation. The excretion of this compound is continuous for a certain period, varying from 3 to 12 days in the cases studied, in 6 of the ten cases the period was 10 to 12 days. Bleeding occurs from 1 to 3 days following its disappearance from the urine. The total amount of pregnanediol excreted per period varied from 3 to 54 mg. The measurement of this compound in the menstrual cycle offers a means of determining the duration and functional activity of the corpus luteum.

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RESPONSES OF THE HUMAN OVARY TO GONADOTROPIC PRINCIPLES

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The ovarian responses to gonadotropic principles have not been the same in any two species of animals investigated. Varying degrees of luteinization of mature follicles with no constancy of ovulation have been observed in the immature mouse following injections of these principles. In the ovaries of the immature rat after similar injections there occurred cystic follicles with little evidence of luteinization. In the rabbit there were cystic and often hemorrhagic follicles. Intravenous injections of these principles produce ovulation in the mature rabbit. Corpora lutea were not produced in the ovaries of the immature Macacus monkey by the use of a single extract, but Engle (1) observed their occurrence following subcutaneous injections of a gonadotropic extract prepared from the anterior lobe of the pituitary followed by the intravenous administration of this extract and a similar one from pregnancy urine.

Studies of the ovaries of the human (2) following the use of pregnancy urine extract and after a gonadotropic principle of anterior pituitary have been described previously. Observations (3) have been reported also on the endometrium in so-called 'endometrial hyperplasia' after treatment with pregnancy urine extracts, with a gonadotropic principle of the anterior lobe and with other principles. We have re-examined recently all the material accumulated to date, made additional investigations and have endeavored to correlate clinical and tissue responses to so-called gonadotropic therapy. These studies were the basis for an analysis (4) of the therapeutic possibilities of these principles. They led also to a summary by one of us (5) of the responses of the human gonads to anterior pituitary-like principles. In reviewing this material we have encountered and corrected the diagnostic errors which occurred in several of the previous reports. These concerned an assumption of anovulatory states existing in 3 patients diagnosed as having "hyperplasia of the endometrium"; our present concepts of endometrial patterns previously described do not warrant such an assumption nor permit the attribution of corpora lutea observed after treatment in these patients to the effects of therapy.

The total material available for analysis at present includes observations upon 85 patients, distributed according to menstrual histories as follows: regular, 22; amenorrhea and oligomenorrhea, 8; menorrhagia, metrorrhagia and polymenorrhea, 51; postmenopause, 2; premenarche, 2. The ovaries of 57 patients were studied either grossly or grossly and microscopically, while in 74 patients the endometrium was studied either alone or in conjunction with the ovaries. Gonadotropic principles from the anterior lobe or from the serum of pregnant mares were employed in 34 patients; similar principles from pregnancy urine or placenta were used in

51 patients. The total doses of the former ranged from 100 R.U. to 4400 M.U., the daily dose varying from 20 R.U. to 800 M.U. Of the pituitary-like principles the total doses varied from 250 R.U. to 24,250 R.U., the daily dose from 100 R.U. to 8000 R.U. The period of treatment lasted from 1 to 87 days. In no instances were ovarian or endometrial changes observed other than those which could be explained by the expected probabilities of the cases.

This report is concerned with a study of the ovaries and of the endometriums or of the endometriums alone of 6 patients with presumed anovulatory bleeding and of those of 1 patient experiencing oligomenorrhea in whom such a diagnosis was not established. These patients received doses of gonadotropic principles derived either from pregnancy urine or from the placenta in larger amounts than those reported previously. We had suggested in previous communications the possibility of differences in the responses of human ovaries to larger doses of these principles. In a recent article Kurzrok (6) also made a similar suggestion.

METHOD OF STUDY

Our method of study in this group of patients comprised a microscopic study of the endometrium before and after treatment and a gross and microscopic study of ovaries after treatment. Ovaries were studied microscopically after serial sectioning and staining with hematoxylin and eosin. Endometriums were studied after the usual hematoxylin and eosin staining and after special staining for glycogen granules. The assumption of an anovulatory state of the ovaries in these cases was founded upon observations and repeated endometrial biopsy studies prior to the initiation of any treatment. The finding of a corpus luteum in the ovary or of localized or generalized progestational response in the endometrium in such patients was considered presumptive evidence of gonadotropic effect.

DATA AND CASE REPORTS

The tissue available for study included ovaries from 3 patients and endometrial specimens before and after therapy in all 7 patients. The total doses ranged from 6000 to 24,250 R.U.; the daily doses from 400 to 8000 R.U. The durations of treatments varied from 1 to 10 days. The patients' ages varied from 15 to 27 years.

Case 1. A white, single, female, aged 15 years, had experienced irregular episodes of amenorrhea and metrorrhagia for 10 months. She gave a history of having received a curettage about 8 months prior to admission with some temporary benefit and had received some injections of a gonadotropic principle of pregnancy urine for 6 days 2 months later with some clinical improvement. The patient had been flowing constantly for 2 months when seen by us. A biopsy of the endometrium made on May 4 showed a phase of estrin arrest. She received 6000 R.U. of a gonadotropic principle (A.P.L./P.U.) on May 4. The temperature rose to 38° C. during treatment. Bleeding stopped on May 7. Studies of an endometrial biopsy taken on May 10 and of a curettage specimen obtained May 12 showed endometriums in a phase of estrin arrest.

Case 2. A white, married, female, para 1-0-1, aged 19 years, had had episodes of metrorrhagia for 4 months. She was admitted to the hospital March 25 at which time she was having severe uterine bleeding and gave a history of having bled

constantly since Feb. 20. Biopsy of the endometrium showed a phase of estrin arrest. She was treated with a gonadotropic principle (A.P.L./P.U.) as follows: March 25, 400 R.U.; March 26 through April 2, 800 R.U. daily, the total dosage being 7000 R.U. There was slight decrease in the amount of bleeding during therapy. A curettement was done April 3 to give the patient a remission from bleeding. Examination of this endometrium showed a phase of estrin arrest. The patient had no further bleeding until May 25 when she began another episode of prolonged and excessive bleeding. She received 1000 R.U. of a gonadotropic principle (A.P.L./P.U.) daily from June 17 to June 23, the total dosage being 7000 R.U. During treatment her bleeding increased sharply. On June 24 she was readmitted to the hospital because of excessive and alarming hemorrhage and received an emergency curettage. Large pieces of tissue 2 cm. in thickness were removed from the uterus. Examination of this endometrium showed marked hyperplasia and a phase of prolonged acyclic estrin action.

Case 3. A colored, single, female of 20 years who had experienced irregular periods of prolonged uterine bleeding since menarche received a gonadotropic principle (A.P.L./P.U.) as follows: August 18, 400 R.U.; August 19, 600 R.U.; August 20, 1100 R.U.; August 21 through August 27, 8700 R.U. The total dose was 9500 R.U. Her last bleeding had started July 16 and continued unabated until curettage on August 21. A biopsy of the endometrium taken on August 18 showed a stage of estrin arrest; curettings on August 21 showed a similar stage; the ovaries at hysterectomy on August 28 showed no corpus luteum.

Case 4. A colored female, aged 23 years, para 1-0-1, had had metrorrhagia of nine weeks' duration when first seen by us. A study of a biopsy of the endometrium taken on May 17 showed a phase of estrin arrest. She received a gonadotropic principle (A.P.L./P.U.) as follows: May 17, 8000 R.U.; May 18, 6000 R.U.; the total dosage was 14000 R.U. The temperature rose to 39.6° on May 17, to 40.3° on May 18 and dropped to normal after treatment was discontinued. Bleeding was decreased very slightly and on May 25 a curettage was done to stop bleeding. Examination of this endometrium showed a phase of estrin arrest.

Case 5. A white, single, girl of 17 years, who gave a history of irregular episodes of prolonged and excessive uterine bleeding for 2½ years, received a gonadotropic principle (A.P.L./P.U.) as follows: April 12, 2000 R.U.; April 13, 4000 R.U.; April 14, 4000 R.U.; April 15, 4000 R.U.; April 16, 4000 R.U. The total dose was 18,000 R.U. The last bleeding had begun on March 8 and lasted throughout the period of therapy. There was a slight decrease in bleeding during the first and second days of therapy but a profuse flow began the last day of treatment and curettage was necessary April 17. An endometrial biopsy on April 12 showed a stage of prolonged acyclic estrin action. The endometrium at curettage April 17, showed a similar stage.

Case 6. A white, married female, aged 27 years, para 7-4-3, who gave a history of oligomenorrhea of several years' duration received a gonadotropic principle (A.P.L./P.U.) as follows: February 4, 3000 R.U.; February 5, 6000 R.U.; February 6, 6000 R.U.; February 7, 6000 R.U. The total dose was 21,000 R.U. Her last menstrual period had occurred December 25, 1936 and lasted 6 days. Her previous menstrual period had started November 6 and lasted 4 days. On February 8 a curettage and laparotomy were done. The endometrium showed a progestational phase with irregular ripening. The right ovary (fig. 1) contained two corpora lutea and the left ovary contained one corpus luteum. The right ovary was studied microscopically. Observations in this case did not permit the assumption that an anovulatory condition existed.

Case 7. An 18 year old, colored, single female with a complaint of metrorrhagia

for 2 years received a gonadotropic principle (A.P.L./P.U.) as follows: March 12, 6000 R.U.; March 15, 6000 R.U.; March 16, 6000 R.U.; March 17, 4250 R.U.; March 18, 1000 R.U. and on March 19, 1000 R.U. The total dose was 24,250 R.U. Her last episode of bleeding had begun on February 4 and had lasted throughout the period of treatment. A study of a biopsy of the endometrium prior to the initiation of treatment showed a stage of estrin arrest (fig. 2). Examination of the endometrium obtained at curettage at the end of treatment (March 20) revealed a similar stage of the endometrium.

Fig. 1. The right ovary of the patient described in *case 6*. Two corpora lutea are observed in this ovary. The left ovary, not removed at operation, contained another corpus luteum. Photograph made before fixation.

DISCUSSION

Ovarian responses, judged either by direct observations at laparotomy, by microscopic study or by inferential studies of the endometrium, were not different qualitatively or quantitatively in this series of patients receiving larger daily and larger total dosage from those in patients reported previously. There occurred no progestational reaction after treatment in the endometriums of the 6 patients with presumed anovulatory failure. Such observations have been taken as presumptive evidence that ovulation and corpus luteum formation had not occurred in these ovaries. In 2 of these patients such inferences were confirmed by direct observation of the ovaries.

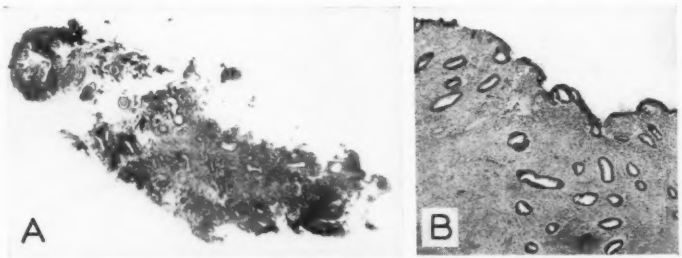

Fig. 2. Endometrial findings in the patient described in *case 7*. *A*) Biopsy, March 12, before treatment: endometrium in an arrested estrin phase (active bleeding). *B*) Curettement, March 20, after treatment with 24,250 R.U. of a gonadotropic principle of pregnancy urine: endometrium in similar phase (active bleeding); no evidence of progestational reaction. X30.

We do not feel warranted in attributing the occurrence of 3 corpora lutea in the ovaries of the patient in *case 6* to the effects of therapy on the basis of the available data. While the corpora lutea appeared individually quite different in their gross and microscopic characteristics, we have not felt justified in hazarding an opinion as to their relative ages. Hartman (7) has called attention to the difficulty and inaccuracy inherent in such attempts. Such a case should stimulate further studies with similar or larger doses.

We are cognizant of the errors inherent in a diagnosis of anovulatory failure. We do feel, however, that the employment of the methods of endometrial interpretation described previously by one of us permits a reasonably safe working clinical diagnosis of such a state. Our inability to observe corpus luteum formation in the ovaries of patients with anovulatory failure is our strongest evidence of the ineffectiveness of such therapy. It may well be, however, that such ovaries due to the mechanical changes occurring in them (thickened tunica, cystic degeneration, etc.) may be unable to respond to such principles.

On the basis of the material available in the 85 cases studied to date, including the 7 reported at this time, the assumption seems warranted that if gonadotropic principles are capable of inducing ovulation and corpus luteum formation in the human, effective pharmacologic doses have not been given as yet. Such a dose probably is in excess of a daily dose of 8000 R.U. or of a total dose of 20,000 to 25,000 R.U.

SUMMARY

An analysis of observations upon 85 patients after gonadotropic therapy and detailed reports of the ovarian responses of 7 patients is made. Six of the 7 cases reported in detail were of patients in whom presumptive diagnoses of anovulatory failure had been made. The total doses in these patients ranged from 6000 to 24250 R.U., the daily doses varying from 400 to 8000 R.U. The observed ovarian responses, judged either by direct inspection of ovaries, by microscopic study of these, or by inferential studies of the endometrium, do not warrant an assumption that ovulation and corpus luteum formation had resulted from such therapy.

We are indebted for generous allotments of the active principles used in these studies to Dr. E. A. Sharp of Parke, Davis & Co., Detroit, Mich., to Mr. Joseph Hutchinson of Ayerst, McKenna & Harrison of Montreal, Quebec, and to Dr. J. A. Morrell of E. R. Squibb and Sons, New Brunswick, N.J. A part of the expenses incurred in these studies was defrayed by a grant from the Research Council of Duke University.

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SOME EFFECTS OF ESTROGENS ON THE UTERUS OF THE MOUSE[1]

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Inflammatory uterine conditions frequently develop in rats and mice receiving large amounts of estrogens for long periods of time (1, 2, 3, 4, 5). Pyometra occurred in all of the mice of one strain which had received weekly injections of 500 I.U. hydroxy-estrin benzoate (3). Animals died showing general peritoneal involvement in less than 20 days in some instances. In other strains uterine inflammatory reactions were not observed when the estrogens were first injected within one week after birth but were occasionally found in animals in which injections were started following weaning.

The periodic leucocytic infiltration of the vaginal epithelium and uterine mucosa in normal mice during the metoestrum has been extensively studied (6). It has been suggested that pyometra or leucocytic invasions occurring in mice receiving estrogens might be due to accentuation of normal physiological changes induced in the tissues by extreme hormonal stimulation. The possibility of bacterial infection under such conditions must also be considered.

In the present study 10 young female mice from the Strong A strain and from 38 to 42 days of age were partially hysterectomized. Approximately the anterior three-fourths of both uterine horns were removed and one horn transplanted subcutaneously lateral to the mid-ventral incision in the inguinal region in each animal. The ovaries were not removed. All of the uterine transplants persisted. The mice were then given weekly injections of 500 I.U. keto-estrin benzoate for from 16 to 32 weeks starting within one week following the operation (table 1). Each mouse received from 8000 to 16,000 I.U. of the hormone. At autopsy the remaining parts of the uterine horns and the uterine grafts were studied.

The uterine grafts quickly became distended with fluid after estrogenic treatment was started and persisted in this condition until removed. At autopsy they were found to be extremely distended, thin-walled and filled with a relatively clear fluid resembling that found in the uteri of normal female mice during early estrum. Histologically the secretion contained very few or no leucocytes (figs. 1 and 3). The epithelium consisted largely of cuboidal or low columnar cells. Occasional tufts of tall columnar cells were observed. The glands were largely parallel with the epithelium lining the central lumen. The muscular and stromal layers were also very thin. In none of the uterine transplants was there any evidence of leucocytic invasion or

[1] This investigation has been supported by the Anna Fuller Fund.

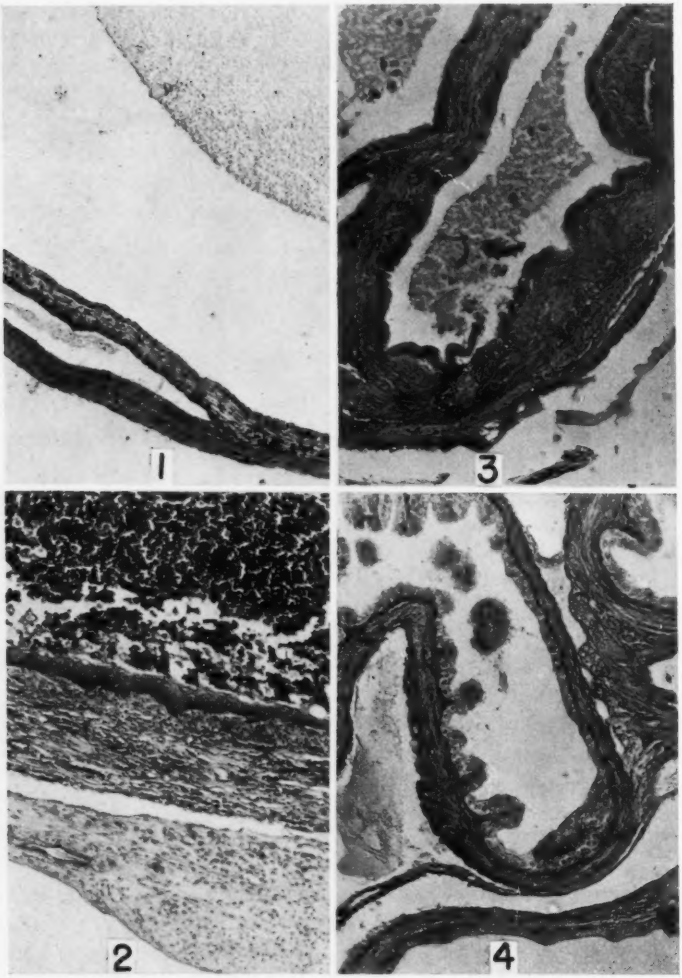

Fig. 1. Section of the uterine wall 229 days after a uterine horn had been grafted subcutaneously in the inguinal region and after 14,000 I.U. of hydroxy-estrin benzoate had been injected at the rate of 500 I.U. weekly. The lumen of the graft contained a clear fluid practically free from leucocytes. The thin wall showed little leucocytic infiltration.

Fig. 2. A portion of the wall of one of the uterine stumps remaining in contact with the cervix from a mouse which had received 13,000 I.U. of hydroxy-estrin benzoate during 203 days. The remaining part of the horns was greatly enlarged and filled with pus. In regions where the epithelium was intact a squamous metaplasia had occurred.

Fig. 3. A portion of the uterine graft of a mouse which had received 13,500 I.U. of hydroxy-estrin benzoate during 266 days. Several weekly injections were omitted because of the poor condition of the animal. The clear fluid in the graft was removed prior to fixation.

Fig. 4. Section of the ovarian capsule and of the distended uterine tubes of the above mouse. The ovary or its adjacent tissues did not show leucocytic infiltration in those mice in which the uterine horns were removed.

pyometra although the cystic distension had persisted for several months.

The remaining uterine stumps of all of the mice were enlarged to varying extents. Some of them had become large encapsulated purulent masses (fig. 2).

In one case death occurred following the development of an extensive peritonitis. In other individuals the remaining portions of the uterine horns were less distended but all showed active pyometra or evidence of inflammation. Adhesions were prevalent in all animals which might indicate a peritoneal extension of the inflammatory condition but surgical controls were not followed. In the more severe pyometras the uterine epithelium was largely destroyed. Slight epithelial metaplasia or cystic hyperplasia occurred in other animals. In one animal an epithelial overgrowth of the cervix,

TABLE 1. INFLUENCE OF ESTROGENS ON UTERINE GRAFTS AND ON THE UTERUS REMAINING IN CONTACT WITH THE CERVIX

Mouse No.	Age operated	Age Inj. started	Period Inj.	Total I.U. Inj.	Condition of	
					Graft	Uterus
	days	days	days			
8	38	44	162	11,500	Clear Cystic	Pyometra
9	38	44	203	13,000	Clear Cystic	Pyometra
11	38	44	266	13,500	Clear Cystic	Fibrotic
13	38	44	136	9,500	Clear Cystic	Pyometra
14	38	44	257	18,000	Clear Cystic	Pyometra
15	42	42	204	14,500	Clear Cystic	Pyometra
16	42	42	216	11,500	Clear Cystic	Enlarged no pus
17	42	42	229	14,000	Clear Cystic	Peritonitis Pyometra
18	42	42	117	8,000	Clear Cystic	Pyometra
20	42	42	236	16,000	Clear Cystic	Small abscess

possibly an early malignant growth, had developed. Similar abnormal growths of the cervix have been observed in other animals (7). The histological findings in these cases were quite similar to those observed in other mice in which the uteri remained intact.

The small yellowish brown ovaries were usually surrounded by distended capsules containing a clear fluid. Inflammatory reactions were not observed in the ovarian capsules of any of the animals (fig. 4). The ovaries were similar to those of unoperated animals under similar treatment. They contained only a few large or small normal follicles and no recognizable corpora lutea. The characteristic color was attributable to a marked increase in lipoid-containing interstitial cells. The ovaries of nonoperated animals and their capsules are very frequently involved in the inflammatory processes. By interruption of the ovarian uterine connections through partial hysterectomy the ovarian capsules became extremely cystic but did not show excessive luecocytic infiltration or abscess formation.

These observations show that pyometra does not develop in the transplanted uterine horn removed from its normal connections with the cervix, though the uterine graft responds to estrogenic hormones. Pyometra develops in the intact uterus or in uterine fragments remaining in contact with the cervix. These observations indicate that estrogenic hormones injected for long periods of time in large amounts induce changes favoring uterine infection

or preventing the control or removal of infection and that pyometra cannot be attributed to a direct action of estrogenic hormones.

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ON THE COMPOSITE NATURE OF THE ESTRUS PHENOMENON[1]

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It has become increasingly evident that the total estrus phenomenon cannot be regarded as a unity, but is composed of a number of integrated reactions in the various organs, and even in the different component tissues of a single organ. This is of more than theoretic significance, since we have recently shown that different estrogenic substances, in comparable doses based on their ability to cause vaginal cornification in the rat, differ markedly in the degree to which they suppress the pituitary in the same animal (1). We have also induced partial or incomplete estrus at certain stages of immaturity in the rat; an estrus reaction in which the vagina and uterine musculature were fully affected, without any signs of endometrial stimulation (2).

These experimental separations of the different phases of the estrus phenomenon suggest the possibility that normally occurring complete estrus may not be due to a single ovarian hormone, but to a number of hormones each of which is especially concerned with a particular phase of the process. Thus we have reported that the incomplete estrus which we observed in immature rats represented their response to an 'incomplete' estrogenic hormone arising from the theca (and interstitia?) of their immature ovaries. As the animals matured, the granulosa gave rise to a more complete estrin, which caused proliferation of the uterine endometrium as well as vaginal and myometrial changes (2). Furthermore, other factors besides the estrins are probably involved. We have shown that even the most generally effective of the estrogenic substances, namely dihydroxyestrin, cannot completely replace the ovary in the induction of certain of the uterine changes of estrus (3). It has therefore been necessary to postulate the elaboration by the ovary of one or more factors which augment or supplement the action of estrin on the uterus.

In the present report the composite nature of the estrus phenomenon is further demonstrated by the separation of certain of its phases by means of x-ray irradiation of the rat.

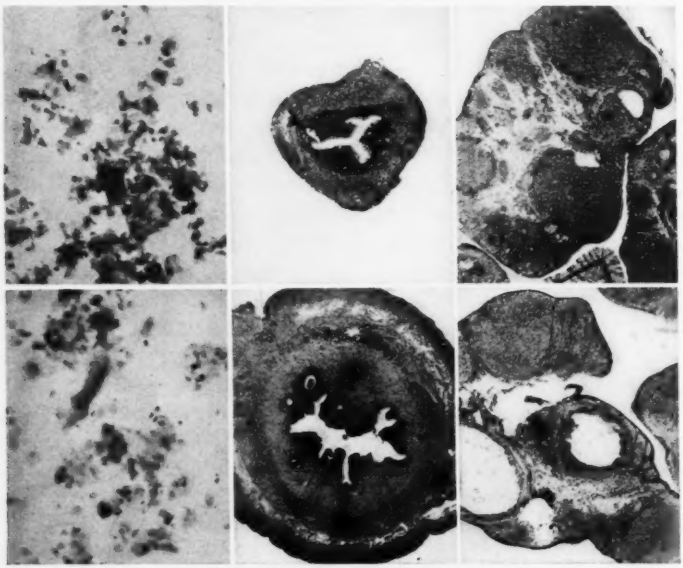
METHOD AND RESULTS

Sixteen female rats of the Long-Evans strain were subjected to x-ray irradiation at the age of 21 days. The animals were placed 10 inches from the target and were treated for 10½ minutes with 5 milliamperes at 110 K.V.P., using a 2 mm. aluminum filter. The total dosage was 450 roentgen units. The

[1] Aided by a Grant from the Committee on Scientific Research of the American Medical Association.

animals were then placed under close daily observation for the appearance of estrous changes.

The vaginal orifices opened at about 45 to 55 days of age. Thereafter, daily vaginal smears indicated the occurrence of fairly regular estrous cycles. After 3 or 4 complete cycles had been observed in each rat, a laparotomy was performed under ether anesthesia at the time of full vaginal cornification. In 9 of the 16 animals the uteri were small and pale, resembling that of the castrate animal; in 4 animals the uteri were moderately distended with fluid; and in only 3 animals did the uteri show the marked hyperemia and distension



Photomicrographs of vaginal smear, uterus and ovary during estrus in an irradiated rat (top row) and a normal control rat (bottom row). Note that, in spite of the full cornification in the vaginal smear, the uterus of the irradiated animal is atrophic. Nevertheless this uterus does show a moderate degree of endometrial proliferation. (Magnifications are identical for the same tissues in each animal.)

of full-blown estrus. The incisions were closed, the animals allowed to recover, and daily vaginal smears were continued. When several cycles had been observed, each rat was again examined during a laparotomy at the time of a full vaginal cornification. At this time 14 of the 16 rats exhibited infantile uteri, while only 2 animals had uterine changes characteristic of estrus. Again the incisions were closed and the animals recovered. A third laparotomy and examination, under the same conditions as above, disclosed no change from the previous examination. Histological examination of sections of the uteri, removed during the last laparotomy, revealed the fact that, in spite of the castrate appearance of the gross specimen, the endometrium had undergone varying degrees of proliferation ranging from cuboidal to the tall columnar epithelium of normal estrus.

We then investigated the possibility that the x-ray irradiation might have acted directly on the uterus to cause the separation of the uterine and vaginal estrus responses and in some cases, the occurrence of endometrial changes in the absence of myometrial effects. The 14 rats which had shown the incomplete estrus were castrated. Six of them were given daily injections of 5 R.U. of dihydroxyestrin benzoate for 3 days. On the 4th day uterine as well as vaginal responses were present, and the uteri of these animals were in moderate estrus as regards both muscle and endometrium, corresponding in degree to that seen in control animals subjected to the same treatment after surgical castration at the age of 25 days. In each of the 8 remaining rats, 2 ovaries from a normal immature rat were implanted. Four of these animals developed irregular vaginal estrous cycles. Examination of the uteri of these 4 animals during a period of vaginal cornification, revealed 3 of them to be in moderate and 1 in full-blown, complete estrus. It is apparent that our results with irradiation were due to an effect on the ovary, and not on the uterus.

Some of the results in the ovaries of our irradiated rats may be of interest. These ovaries were about half normal size and contained corpora lutea of varying sizes, and of fairly normal histologic appearance, except for some decreased vascularity. However, the follicular apparatus appeared to be severely damaged. Practically no small follicles were seen. Some sections contained no follicles at all, but most sections showed 1 or 2 medium to large-sized follicles. There were present, in addition, varying amounts of a large, lutein-like cell, with poorly staining cytoplasm, similar to the 'epithelioid cells' described by Parkes (4) in the ovaries of irradiated mice. However, in our rats these cells were often grouped about an old follicular cavity, and seemed to arise directly from the theca, instead of from the germinal epithelium, as in Parkes' mice.

Parkes' mice also differed from our rats in yielding a complete uterine estrus. Levine and Witschi (5) have also reported the occurrence of a more or less complete uterine estrus in irradiated rats. The difference between these results and our own may possibly be due to the species of animal used, the age at which irradiation was done, or the type and amount of irradiation used.

DISCUSSION

Female rats which had been subjected to x-ray irradiation at 21 days of age, subsequently developed an incomplete type of spontaneous estrus. The vagina was fully cornified, but the uterus presented grossly a castrate appearance. In some cases, the uterine endometrium was more or less proliferated but the uterine wall showed little or no hyperemia or hypertrophy. These results may be contrasted with our previous work (2) in which, following the injection of APL into infantile rats, we observed an estrus in which the vagina was fully cornified, the uterine wall was hypertrophied, but the uterine endometrium remained in its infantile state. Control experiments, in both the present and the previous work, showed that the uterus was capable of yielding a complete estrus response to injected estrogenic substance. The separation of the vaginal and uterine responses on the one hand, and of the

endometrial and myometrial phases on the other hand, must therefore be ascribed to a lack of one or more of the several ovarian factors or hormones, which ordinarily act in conjunction to produce complete normal estrus.

The fact that our animals, in the present experiments, appeared to have a normal estrous cycle as judged by the changes in the vaginal mucous membrane, has important practical implications. It is clear that the widely used Allen-Doisy vaginal smear technique, while it constitutes a convenient index of the occurrence of the estrous cycle, may give no indication of concurrent functional ovarian abnormalities. It would seem advisable to regard the use of the human vaginal smear (6, 7) with similar reservations, until proven otherwise. Our results may also help to explain the frequent lack of correlation between the estrin titre of blood and urine and the clinical syndrome, in cases of ovarian dysfunction. It is suggested that such quantitative assays might be less disappointing if supplemented by some qualitative estimation of the physiologic properties of the estrogenic substances present.

SUMMARY

The composite nature of the estrus phenomenon has been demonstrated in irradiated rats. It has been shown that even cyclic vaginal cornification does not necessarily indicate normal ovarian function. The application of these results to laboratory and clinical work is briefly indicated.

We are indebted to the Dept. of Roentgenology, Michael Reese Hospital, for the irradiation of our animals.

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THE EFFECT OF GRADED DOSES OF ESTRIN UPON THE PITUITARY, ADRENAL, AND THYMUS WEIGHTS OF MATURE OVARIECTOMIZED RATS[1]

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The influence of estrogenic substances upon the hypophysis, adrenals, and thymus glands of normal and gonadectomized animals has received considerable attention in recent years. Some of these investigations, using the rat as experimental animal, are very briefly summarized below.

Great variation in the length of castration or injection periods, potency of the estrogen used, dosage, age and strain of the rats, and individual differences in techniques used are some of the factors which possibly explain the differences in results. The present study was undertaken to investigate the effects of several different doses of estrogen upon pituitary, adrenal, and thymus gland weights.

MATERIALS AND METHODS

One hundred fifty-three mature virgin female albino rats of the highly-inbred Sprague-Dawley strain, ranging in weight from 186 to 269 gm., and from 5 to 7 months in age, were separated into 6 groups. Of these, 36 were left untreated and served as normal controls. The rest were castrated by the method of Schultz (26). Ten of these, designated as *A* castrates, averaging 219 gm. at castration, were injected daily for 19 days with 0.05 cc. of sesame oil. Three groups, 16, 16, and 18 in number, and each averaging 222 gm. at castration, were injected daily with 0.25, 0.50, and 5.0γ of dihydroxyestrin,[2] dissolved in 0.05 cc. of sesame oil, for the same period as the *A* castrates. All injections were begun 24 hours after castration, and autopsies were performed on the day following the last injection. These experiments were carried out in January and February, 1937. In May and June, 1937, a group of 57 rats was ovariectomized and left untreated for the same period as the above groups. These constitute the *B* castrate group.

The crystalline dihydroxyestrin was stated by the Schering Corporation to have a potency of 12.5 R.U. (Allen-Doisy) per γ, and a melting-point of 172 to 174° C. Both statements were found to be correct by tests conducted in our laboratory. Hence, the estrin-treated groups received approximately 3.1, 6.2, and 62.5 R.U. per day, respectively.

All animals were weighed before autopsy and sacrificed by rapid decapita-

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[2] The dihydroxyestrin in crystalline form and the sesame oil were generously furnished through the courtesy of Dr. G. Stragnell of the Schering Corporation.

Investigator and date	Sex	Age	Effect of treatment on organ weights: Pituitary	Adrenals	Thymus
Effect of Castration					
1915. Hatai (1)	M	Adult & Im.	Increase	Increase	Increase
	F	A & Im.	Sl. incr.	Decrease	Increase
1930. Kinugasa (2)	M & F	Im.	—	—	No change
	M & F	A	—	—	Increase
1933. Andersen & Kennedy (3)	M	Im.	Increase	Increase	—
	M	A	Increase	No change	—
	F	Im.	No change	No change	—
	F	A	No change	Decrease	—
1935. Andersen (4)	F	A	Decrease	Decrease	—
1935. Freudenberger & Billeter (5)	F	A	No change	Decrease	Increase
1936. Bühler (6)	F	Im.	—	—	Increase
1936. Halpern & D'Amour (7)	F	A	Sl. incr.	—	—
1936. Lawless (8)	M	A	Increase	Increase	Increase
1936. Winter & Emery (9)	M	A	—	Increase	—
	F	A	—	Decrease	—
1937. Billeter (10)	F	A	Decrease	Decrease	Increase
Effect of Estrin upon Castrates					
1933. Leiby (11)	F	A	Increase	Increase	No change
1934. Korenchevsky & Dennison (12)	M	A	Increase	—	Decrease
1935. Andersen (4)	F	A	Increase	Increase	—
1936. Ellison & Burch (13)	F	A	Increase	Increase	—
1936. Grumbrecht (14)	F	A	Increase	—	—
1936. Halpern & D'Amour (7)	F	A	Increase	—	—
1936. McEuen, Selye, & Collip (15)	M & F	A	Increase	Increase	—
1936. Nelson (16)	F	A	Increase	No change	—
1937. Wolfe (17)	F	A	Increase	—	—
Effect of Estrin upon Normals					
1928. Golding & Ramirez (18)	M & F	Im.	—	—	Decrease
1931. Leonard, Meyer, & Hisaw (19)	F	Im.	No change	No change	No change
1934. Korenchevsky & Dennison (12)	M	A	Increase	Increase	No change
1935. Selye, Collip, & Thomson (20)	F	Im.	No change	No change	—
	F	A	Increase	Increase	—
1935. Shumacker & Lamont (21)	F	Im.	—	No change	—
1935. Wolfe (22)	F	A	Increase	—	—
1936. Bühler (6)	F	Im.	Increase	—	Decrease
1936. Halpern & D'Amour (7)	F	A	Increase	—	—
1936. Nelson (16)	F	A	Increase	Increase	—
1936. Zondek (23)	F	A & Im.	No change	No change	—
1936. Zondek (24)	M	A & Im.	Increase	Increase	—
1937. Freudenberger & Clausen (25)	F	Im.	Decrease	Decrease	No change
1937. Wolfe (17)	F	A	Increase	—	—

tion. The adrenals and thymi were removed immediately, dissected free of investing tissue, and weighed. The hypophyses were aseptically removed and weighed and assayed for gonadotropic potency. These results will be reported later in another paper. After the mean weights were determined, the standard deviations of the distributions were calculated from the formula

$$\sigma\ dis. = \sqrt{\frac{S(\bar{x}-x)^2}{N}}.$$

The standard error of the mean was calculated from the formula:

$$\sigma\ mean = \frac{\sigma\ dis}{\sqrt{N-1}}.$$

The significance of the difference of the means was found by dividing the difference by the standard error of the difference (calculated from the formula, $\sigma\, diff. = \sqrt{\sigma^2\, mean_1 + \sigma^2\, mean_2}$). The probability that the difference of the means is due to chance, and is therefore not a true difference, was obtained from the table of X, given by Fisher (27), in the appendix of the book. For example, a probability (P) of 0.01 means that in 1 case in 100 a difference as great as that observed would be expected to occur by chance. We feel that expressing the results in terms of probability is less arbitrary and more accurate than merely stating that a difference is significant if it exceeds 2 or 3 times its standard error, or 3 or 4 times its probable error.

RESULTS

The mean weights of the pituitary, adrenals, and thymus and their respective standard errors, together with the standard deviations of the distributions, are presented in table 1. Table 2 gives the differences between the means of each group compared with every other group, the standard error of the differences, the quotient of difference divided by standard error of the difference, and finally the probability (column headed by P) that the obtained difference is due to chance. The charts give a graphic comparison of the mean gland weights.

TABLE 1. MEAN GLAND WEIGHTS WITH THEIR STANDARD ERRORS (*S.E.*) AND STANDARD DEVIATIONS OF THE DISTRIBUTIONS

Group	No. rats	Body Weight		Pituitary Weight		Adrenal Weight		Thymus Weight	
		At Cast.	At Autop.	Mean ± *S.E.* (mg.)	Std. Dev.	Mean ± *S.E.* (mg.)	Std. Dev.	Mean ± *S.E.* (mg.)	Std. Dev.
Normal	36	—	214	13.4±0.26	±1.53	60.0±1.27	± 7.55	191± 5.4	±31.9
A Castrate	10	219	238	12.4±0.37	±1.11	50.3±2.39	± 7.16	305±13.7	±41.2
B Castrate	57	—	260	13.4±0.15	±1.13	60.2±0.99	± 7.41	378±11.6	±87.0
0.25γ	16	222	230	17.2±0.49	±1.89	61.8±2.03	± 7.86	205±12.4	±48.0
0.50γ	16	222	226	17.4±0.41	±1.58	61.4±2.81	±10.87	198±16.2	±62.9
5.00γ	18	222	220	19.8±0.70	±2.87	58.9±1.43	± 5.89	140±10.2	±42.2

Pituitary. Injection of estrin into the castrated female leads to unquestionable hypertrophy of the hypophysis, being greatest in the group receiving the largest dose of the hormone (5.0γ). There is a statistically significant difference between the mean weights of the normals and castrates, on one hand, and the estrin-treated groups, on the other. Similarly, the means of the 0.25 and 0.50γ groups differ significantly from that of the 5.0γ group. There is no difference between the two low dose groups. The pituitaries of the *A* castrates, which served as controls for the estrin-treated groups, weighed significantly less than the *B* castrates and normals, according to the statistical methods used. However, as Fisher (27) has shown, these formulas become inaccurate when applied to a sample as small as 10 measurements. We therefore hesitate to interpret this difference as indicating pituitary atrophy as a result of a 20-day period of castration. Since the body weights of the B castrates averaged 22 gm. heavier than the *A* castrates at autopsy (see table 1), heavier pituitaries might conceivably be expected in the former group. This being the case, gland weight/body weight ratios can be used to correct

part of the difference. The mean ratios are 52.0 and 51.0 mg./kg. for the *A* and *B* groups, respectively. This correction is not entirely valid, however, for several reasons: (*a*) difference in season; (*b*) difference in treatment, the A group having been injected with oil; and (*c*) for reasons discussed below under the adrenals. None of these factors was sufficiently controlled to permit us to explain correctly the apparent difference between the two groups of castrates. Hence, our conclusion must be that a 20-day period of castration has little or no effect on the pituitary weight of mature female rats.

Adrenals. Within the limits of this experiment, ovariectomy and estrin treatment are without significant effect on the absolute adrenal weights. If the results on the small group of *A* castrates are considered completely reliable, 20 days of castration may be interpreted to cause a slight adrenal atrophy. In this case, the estrin treatment may be considered to have maintained the

TABLE 2. SIGNIFICANCE OF THE DIFFERENCES OF THE MEANS, EXPRESSED AS THE PROBABILITY (*P*) THAT DIFFERENCE IS DUE TO CHANCE

Groups Compared	Pituitary				Adrenals				Thymus			
	Diff. of Means	σ diff.	Diff. / σ diff.	P	Diff. of Means	σ diff.	Diff. / σ diff.	P	Diff. of Means	σ diff.	Diff. / σ diff.	P
Normal—*A* Castrate	+1.0	±0.45	0.22	.03–.04	+9.7	±2.71	3.58	<.01	−114	±14.8	7.7	<.01
Normal—*B* Castrate	0.0	±0.30	0.00	—	−0.2	±1.62	0.12	.90	−187	±12.8	14.7	<.01
Normal—0.25γ	−3.8	±0.55	6.87	<.01	−1.8	±2.40	0.75	.46	− 14	±13.5	1.0	.30
Normal—0.50γ	−4.0	±0.48	8.27	<.01	−1.4	±3.08	0.45	.65	− 7	±17.1	0.4	.68
Normal—5.00γ	−6.4	±0.74	8.62	<.01	+1.1	±1.92	0.57	.57	+ 51	±11.5	4.4	<.01
A Castrate—*B* Castrate	−1.0	±0.40	2.49	.01–.02	−9.9	±2.58	3.83	<.01	− 73	±18.0	4.1	<.01
A Castrate—0.25γ	−4.8	±0.61	6.97	<.01	−11.5	±3.13	3.67	<.01	+100	±18.5	5.4	<.01
A Castrate—0.50γ	−5.0	±0.55	9.05	<.01	−11.1	±3.68	3.01	<.01	+107	±21.3	5.0	<.01
A Castrate—5.00γ	−7.4	±0.79	9.38	<.01	−8.6	±2.72	3.16	<.01	+165	±17.1	9.6	<.01
B Castrate—0.25γ	−3.8	±0.51	7.43	<.01	−1.6	±2.26	0.71	.48	+173	±17.0	11.4	<.01
B Castrate—0.50γ	−4.0	±0.44	9.19	<.01	−1.2	±2.98	0.40	.69	+180	±20.0	9.0	<.01
B Castrate—5.00γ	−6.2	±0.71	8.71	<.01	+1.3	±1.74	0.75	.46	+238	±15.5	14.7	< 01
0.25γ—0.50γ	−0.2	±0.64	0.31	.75	+0.4	±3.46	0.12	.91	+ 7	±20.4	0.3	.73
0.25γ—5.00γ	−2.6	±0.85	3.06	<.01	+2.9	±2.49	1.16	.25	+ 65	±12.6	5.2	<.01
0.50γ—5.00γ	−2.4	±0.80	2.97	<.01	+2.5	±3.04	0.82	.41	+ 58	±19.2	3.0	<.01

glands at normal weight levels. The same conclusion could be drawn from comparison of the relative adrenal weights (gland weight/body weight). Expressed in this way, the *A* and *B* castrate groups have relative weights of 211 ± 9.1 mg./kg., and 231 ± 3.9, respectively, thus differing significantly from the normals, 0.25, 0.50, and 5.0γ groups, which have relative weights of 279 ± 5.4, 266 ± 8.1, 271 ± 10.0, and 266 ± 7.2 mg./kg., respectively. This sort of comparison proved not to be valid, however, since in no group except the normals, did the coefficient of correlation between adrenal weight and body weight reveal a significant positive correlation. This loss of correlation after castration can be explained on the following grounds: *(a)* castration of the mature female rat leads to variable body weight increases, while *(b)* estrin tends to suppress this increase, also in a variable manner; *(c)* both of these procedures, therefore, add variables, affecting chiefly the body weight factor, which disturb the correlation normally existing between adrenal and body weights. We therefore assert that unless significant correlation exists between body weight and organ weights in all experimental groups, gland weight/body weight ratios cannot validly be compared.

In view of these considerations, we feel that some of the conclusions reached by Andersen and Kennedy (3), concerning especially their group of

mature spayed females (XIII *A* & *B*), may be somewhat overdrawn, since they are based upon comparisons between relative weights of the adrenals of normal and spayed rats. These authors conclude that a 21-day period of castration leads to definite atrophy of the adrenals, but examination of the absolute weights does not give so definite an impression. Their data on the longer periods of castration, however, show definite absolute weight decrease. The number of rats in their groups was usually too small, in our opinion, to measure accurately the changes in the weight of a gland which shows so great a normal variation as does the adrenal.

Thymus. There is no significant difference between the mean thymus weights of the normals and the castrated groups receiving 0.25 and 0.50γ of estrin. Hence, 3 to 6 R.U. per day prevent thymus weight changes in the castrated female rat. There is a marked hypertrophy of the thymus in the two castrate control groups, being more pronounced in the *B* group. The

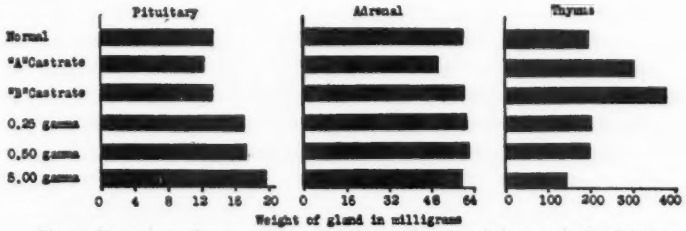

Fig. 1. Comparison of mean weights of pituitary, adrenal, and thymus glands of mature normal, castrated, and estrin-treated castrate female rats. Length of castration and injection period—20 days. Dose—0.25, 0.50, 5.04 (3.1, 6.2, and 62.5 R.U.) per day.

thymi of the 5.0γ group atrophied to a level significantly below the normal and low-dose groups. The difference between the means of the two castrate groups must again be explained on the grounds discussed above under the pituitary, and is subject to the same limitations.

Effect on Body Weight. Injection of estrin into castrates prevented some of the usual body weight increase. Reference to table 1 shows that the *A* castrates and the 3 estrin-treated groups had nearly the same mean body weights at the time of castration, while at the end of the 20-day period, the castrates had gained an average of 19 gm., the 0.25γ group averaged a gain of 8 gm., the 0.50γ group increased by 4 gm., and the 5.0γ group lost an average of 2 gm. Although there is considerable overlap in the body weight distributions, the difference between the *A* castrates and the 5.0γ group is clearly significant, the probability being less than 0.01 that the difference is due to chance. This agrees with the findings of Freudenberger and Clausen (25), Spencer, D'Amour, and Gustavson (28), Zondek (29), Korenchevsky and Dennison (12), Billeter (10), and others.

In general, the findings herein reported confirm the results of most of the investigators cited above. The effects of estrogenic treatment on the weight of the pituitary seem well established. That the thymus of the adult, post-puberal spayed rat actually hypertrophies rather than exhibits merely a delayed involution seems likewise well established. It seems clear that the

adrenal weight is far less sensitive to castration and estrin treatment than are the hypophysis and thymus weights.

SUMMARY

The average pituitary and adrenal weights of 67 mature female albino rats were not changed by a 20-day period of castration, when compared to those of 36 normal females of the same age and weight range. In 2 groups of female rats 20 days of castration led to marked hypertrophy of the thymus gland, averaging 60 and 100 per cent above normal levels, respectively.

Injection of 0.25, 0.50, and 5.0γ (3.1, 6.2, and 62.5 R.U.) of dihydroxy-estrin (Schering) daily for 19 days immediately following castration caused distinct pituitary hypertrophy, averaging 28, 32 and 46 per cent above normal and castrate control levels, respectively.

Treatment with the above doses of estrin for 19 days did not alter the adrenal weights of castrated mature females. The smaller doses of estrin prevented castration hypertrophy of the thymus. The larger dose (5.0γ) caused atrophy of the gland approximately 25 per cent below normal and low dose levels.

Gains in body weight during the castration and injection period for the castrated controls, and the 3 estrin-treated groups averaged as follows: castrate, 19 gm.; 0.25γ group, 8 gm.; 0.50γ group, 4 gm.; and 5.0γ group, lost 2 gm.

The authors are indebted to Dr. J. A. E. Eyster of the Department of Physiology and to Professor H. P. Evans of the Department of Mathematics for their assistance with the statistical analysis herein presented.

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THE EXCRETION OF ANDROGENIC AND ESTROGENIC SUBSTANCES IN THE URINE OF CHILDREN[1, 2]

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With the introduction of adequate quantitative methods for the extraction of sex hormones from urine, it becomes feasible to investigate the presence of these substances in the urine of children. The purpose of this paper is to present in preliminary form the results of our study of this problem.

The urines assayed were individual specimens obtained from children who ranged in age from 6 to 16 years and represented the total urinary excretion of each child for periods varying from 24 to 168 hours. They were collected under careful supervision, in order to insure that all the urine voided during the period of observation would be included in the sample.

The method for the quantitative extraction of androgenic and estrogenic substances employed in this study has been previously described (1). Our only deviation from the procedure as described was to reduce the length of the hydrolysis from 2 hours to 15 minutes. It has recently been found that this modification increases the yield of androgenic material by from 35 per cent to 78 per cent (2).

The estrogenic activity of the urines was assayed on the adult spayed rat by the vaginal smear technique (3), and the results expressed in terms of the estrogenic activity of known quantities of estrone. The androgenic activity was assayed by means of a new technique which is based on the increase in the weight of the comb of the day-old, white leghorn chick following the injection of androgenic material. (4, 5). The urinary extract to be assayed is dissolved in olive oil and injected subcutaneously into the test animals. The observed increase in the comb weight, which reflects the androgenic activity of the extract, is expressed in terms of the quantity of androsterone required to produce a corresponding weight increment. Chicks from a carefully selected, homogeneous stock[3] were used throughout these studies. A detailed description of this assay method will be published in the near future.

The urinary assays of the boys and girls studied are listed in table 1, in which the cases are arranged in the order of chronological age. It will be noted that androgenic activity was found in the urine of all the children in

[1] Read before the 21st Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N.J., June 8, 1937.

[2] Aided by a Grant from the General Education Board of the Rockefeller Foundation.

[3] The chicks were supplied by Hall Bros. Hatchery, Wallingford, Conn.

amounts varying from 1.1 to 32 International Units per 24 hours. The estrogenic activity observed ranged from less than 5 to 95 I.U. for the same period.

It is apparent from the table that the androgenic and estrogenic activities of the urines vary in puberal boys of the same chronological age. Cases 5 and 14, for example, are boys whose hormone excretion was considerably greater

TABLE 1.

Case No.	Age	Androgenic Activity (I.U.[1] per 24 hr.)	Estrogenic Activity (I.U.[1] per 24 hr.)
	BOYS		
1	7 yr. 9 mo.	1.1	<9.0
2	9 yr.	2.0	<5.0
3	11 yr.	2.0	15.0
4	11 yr.	2.0	10.6
5	13 yr. 2 mo.	15.0	48.0
6	13 yr. 2 mo.	1.2	9.0
7	13 yr. 2 mo.	4.0	12.0
	13 yr. 2 mo.	1.5	12.0
	13 yr. 3 mo.	3.5	10.2
8	13 yr. 3 mo.	5.3	24.0
9	13 yr. 4 mo.	8.0	13.0
	13 yr. 7 mo.	10.8	20.0
10	13 yr. 6 mo.	8.0	10.0
11	14 yr. 3 mo.	7.0	—
12	14 yr. 8 mo.	16.5	38.0
13	15 yr. 1 mo.	6.0	18.0
14	15 yr. 4 mo.	32.0	67.0
15	15 yr. 9 mo.	20.0	65.0
16	15 yr. 10 mo.	8.4	24.0
	16 yr. 1 mo.	14.0	30.0
17	16 yr. 2 mo.	14.0	95.0
18	16 yr. 3 mo.	19.0	68.0
	16 yr. 3 mo.	15.0	79.0
	16 yr. 4 mo.	19.0	68.0
	GIRLS		
19	7 yr. 8 mo.	2.0	—
20	9 yr.	0.7	10.0
21	10 yr. 11 mo.	2.2	5.6
22	11 yr.	3.0	<5.0
23	12 yr.	7.0	20.0

[1] The International Unit of androgenic activity is that evoked by 0.1 milligram of androsterone. The I.U. of estrogenic activity is that evoked by 0.1 microgram of estrone.

than that of the others in their respective age groups. These two boys, however, were more mature physically than their contemporaries. Since, as is well known, puberal girls of the same chronological age also differ markedly in the degree of their physical development, one may expect comparable differences in their hormone excretion. These considerations indicate the inadequacy of chronological age alone as a criterion of maturity. They emphasize also the need for caution in interpreting the results of assays of pooled samples from children of the same chronological age, if the latter differ markedly in their developmental status. Because of this variation between children of the same age, it follows that the assay values for the various age groups in our

study are not necessarily the same as those which may be found for other children of the same age.

In view of the marked variation in the developmental status of children of the same chronological age, it seems desirable to attempt to relate the sex hormone excretion more directly to the degree of physical maturity. An extensive investigation of this relationship is now in progress in our laboratory.

SUMMARY

The urines of 18 boys and 5 girls, ranging in age from 6 to 16 years, were assayed for androgenic and estrogenic activity. The androgenic activity varied from 1.1 to 32 I.U. per 24 hours, while the estrogenic activity ranged from less than 5 to 95 I.U. for the same period. Attention is called to the difference in the sex hormone excretion of children who, though of the same chronological age, differ from each other in the degree of their physical maturity.

Addendum: Dingemanse, Borchardt, and Laqueur (6) reported finding comb growth-stimulating material in the pooled urines of both 5-year-old boys and girls and also in individual samples from 6 boys and 3 girls. This paper came to our attention after the assays reported here had been completed.

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INDUCTION OF PENILE ERECTION BY MALE HORMONE SUBSTANCES

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Male hormone substances are responsible for growth, maintenance, and function of the male reproductive tract. This communication deals with their rôle in regard to the penile erection necessary for intromission and completion of the sexual act of copulation in animals and in man.

Animal Study. Penile growth and the capacity for erection were studied before and after the injection of male hormone substances, testosterone acetate[1] and testosterone propionate[1] in immature rodents and monkeys. Figures 1, 2 and 3 show that male hormone substances in immature male monkeys of 1 to 2 kg. not only produced growth of the whole reproductive tract and associated glands, but also stimulated erections. Such erections were aroused spontaneously or produced by contact with some external object. Even in female animals receiving male hormone substances, there occurred clitoridean growth to penile proportions and histological characteristics (1). In the monkey, the protuberant character of the clitoris was especially striking (fig. 4 and 5). Moreover, in the rodent the preputial glands, which in male animals secrete an oily substance lubricating the shaft of the penis, were stimulated in the female to produce a similar secretion at the clitoris (2).

The opposite condition to that produced by injection of male sex substances was obtained by castration and hypophysectomy of rodents. The penis decreased somewhat in size and within a short time erection and copulation appeared to occur infrequently. If the castrated or hypophysectomized animals received male hormone substances, genital maintenance, erections and copulative attempts were continued with fertilization of female animals (3, 4).

Human Studies. The capacity for erection was investigated in persons receiving male hormone treatment in various conditions. These included 5 cryptorchid children, ranging from 18 months to 11 years in age, a 26-year-old hypogonadal case, a 15-year-old boy, normal save for severe acne, and a 43-year-old man with complete impotence for the past 8 years.

The cryptorchid children received from 2.5 to 10 mg. of testosterone propionate in peanut oil 3 times weekly, injected subcutaneously, the dosage in an individual depending upon body weight. Before much growth of genitalia or pubic hair was obtained a tendency to erection was apparent. Parents of children commented upon the phenomena in all children treated

[1] Perandren, furnished through the courtesy of the Ciba Company.

with male hormone substance. The erections lasted for 20 minutes in one child.

The 26-year-old hypogonadal patient had experienced only very infrequent erections prior to treatment. The penis was 2.5 cm. long and 1.3 cm. in diameter. The growth following male hormone administration has been described elsewhere (5). Within 60 hours after his first injection, erections occurred. Throughout a month's treatment with a total of 550 mg. of

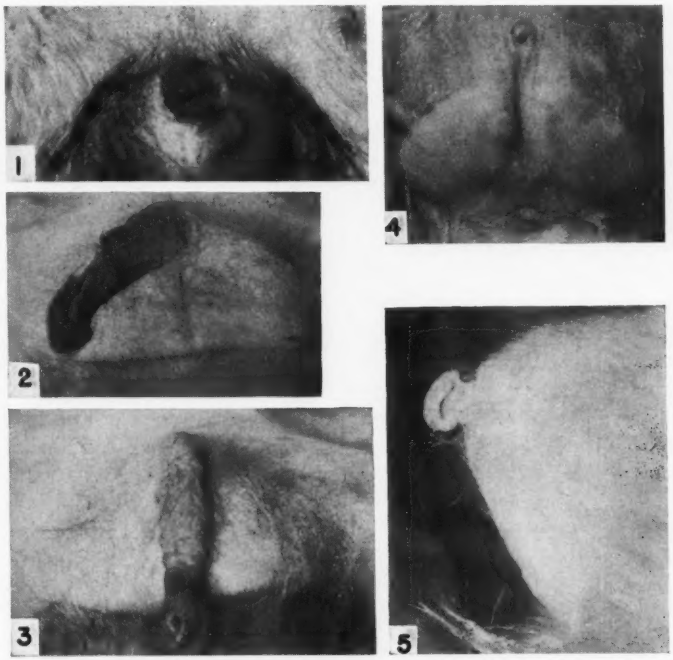

Fig. 1. Penis of control monkey (Macacus rhesus).
Figs. 2 and 3. Penis of monkey receiving injections of testosterone propionate. Note the erection.
Fig. 4. Perineal view of control monkey showing small clitoris lying within vulval folds.
Fig. 5. Side view of monkey injected with testosterone propionate. Note the well-developed glans and body of the projecting clitoris.

testosterone acetate in peanut oil (injections 3 times weekly) a continual series of erections occurred and at time bordered upon priapism. Administration of a bland solution, which the patient believed to contain hormonal material, was followed by a marked decrease in the number of erections. Upon cessation of the injections for 1½ months, erections became as infrequent as before treatment. Resumption of male hormone injections with a dosage of 5 mg. of testosterone propionate 3 times weekly was relatively ineffective; only when a higher body level was reached did erections occur as before. A 15-year-old boy receiving the same small dosage of 5 mg. of testosterone propionate in peanut oil 3 times weekly reported no unusual erections.

The following case history is given because of the definite benefit obtained in a patient exhibiting a pronounced condition of impotence which had prevented marital intercourse for a period of 8 years prior to treatment. A 43-year-old white male, in whom no organic cause could be found for impotence, had acquired complete and lasting impotence after a period of maladjustment due partially to a small introitus of the wife. The patient received a solution containing only an oil vehicle 3 times weekly for 2 weeks; no erections were obtained. To the same oil vehicle was then added 5 mg. of testosterone acetate given 3 times weekly for 3 weeks. No erections were obtained. After a lapse of treatment for a month, injections of 20 mg. of testosterone propionate in the same vehicle were administered 3 times weekly. After 3 injections the patient reported the occurrence of spontaneous erections, while he slept or carried on his daily work. After 6 injections, intercourse was successfully carried out twice in 1 week.

DISCUSSION

In any question of impotence the mental factor is variable and extremely difficult to evaluate. It seems, therefore, that the data in this present report are rendered more significant by the fact that the rôle played by any mental factor is minimized in immature animals and in young children. It should be entirely absent in an 18-month baby. Moreover, erections could be elicited by handling of the penis in injected immature monkeys, even when they were under light anaesthesia. Striking, too, was the rapid post-injection onset of erections in the hypogonadal patient, who had almost a total inability of erection previous to treatment. The disappearance of these erections when bland material was injected, even when the patient believed the solutions to be potent, and the reappearance of erectile capacity only when treatment with adequate dosage was resumed, tend to show the direct physiological effect of these synthetic male hormone substances distinct from the influence of mental attitude.

In the 43-year-old patient with impotence for many years no erections were induced by oil solutions and psychotherapy, or by a solution too weak to produce erections in the boy suffering from acne. But dosages of 20 mg. of testosterone propionate 3 times weekly produced involuntary erections, not always when desired by the patient, but often at unusual hours, while asleep or at work, when his thoughts were not directed toward sexual matters. Noteworthy too, were his statements that the erections did not subside after ejaculation.

Further evidence of male hormone stimulation of penile erections in humans is given by Koch (6) who observed such stimulation in 2 hypogonadal cases receiving extracts of testis tissue. In pubertas praecox in boys, a condition in which large amounts of male hormone are present at an early age, erections have been observed within the first year of life (7). Children to whom anterior pituitary-like substances have been given are reported (8) to exhibit marked erectile tendencies. This could be interpreted as due to production of male hormone substances by the testes (9), since these gonado-

tropic substances do not stimulate the genitalia in the absence of the gonads.

In summary, animals and, if the hypogonadal cases seen by the author are typical, humans too, lacking the male hormone necessary for genital growth may have a lessened capacity for penile erections. Conversely, animals and humans receiving large amounts of male hormones by injection or consequent to abnormal endocrine conditions, have a greatly increased capacity for penile erections.

Therefore, it seems that male hormone substances may be of value in the treatment of impotence. Strong emphasis must be placed, however, upon the necessity of recognizing mental factors in all studies aiming to evaluate such therapy. Preliminary treatment with impotent solutions administered along with psychotherapy should aid in differentiating effects due to administered male hormone from those due to other influences. Further, it must be realized that patients who presumably have a low content of male hormone substance are capable of some amount of penile erection, as shown by the hypogonadal patient before treatment, and by eunuchs. Indeed, a man castrated for 25 years has been reported to carry on satisfactory marital relations (10), and McCartney (11) found 10 cases of gonorrhea in a series of 23 eunuchs. This capacity for erection in the absence of gonadal secretion is in agreement with animal data wherein guinea pigs have copulated months after castration (12).

The choice of hormone now available for use in obtaining this response will lie between anterior pituitary-like and male hormone substances, for theoretically the former material should act indirectly by stimulating the testes to produce male hormone. It is the opinion of the author that, at present, synthetic male hormones are preferable to extracts of anterior pituitary-like substances. Male hormone substances, testosterone acetate and testosterone propionate, are synthetic, stable chemicals; anterior pituitary-like substances are extracts whose potency may change and is not in all instances that labelled on the bottle (13). Anterior pituitary-like extracts have been known to produce unwanted side effects. Two cases of febrile reaction, nausea, and vomiting, one with bilateral hemianopia, have occurred recently at Albany. An editorial warning was issued by the Journal of the American Medical Association concerning the production of cystic ovaries by these extracts (14). On the other hand, there has been insufficient experience and elapse of time in the use of these potent male substances to eliminate possible dangers. In chemical structure they, like female hormones, are similar to known carcinogenic agents. The most that can be said now is that preliminary studies on animals and humans have not given evidence of carcinogenic action. Anterior pituitary-like substances act only indirectly through stimulation of the gonads and therefore depend upon a responsive testis for production of the necessary male hormone. Administration of male hormone is in itself effective and would be expected to function even in hypogonadal and castrate conditions.

In the selection of male hormones synthetic material is to be preferred to extracts (6). Testosterone is the most potent synthetic substance and in

the propionate form is absorbed but slowly (15); therefore, it has the greatest androgenic effect. Vehicles such as peanut oil make for slow absorption, hence a lasting potent effect. In the results reported here injections were given 3 times weekly, but this may be more often than necessary, since testosterone propionate in peanut oil is but slowly absorbed. Daily urine analyses of patients under treatment would go far towards defining this point.

The question of the effect of male hormones on spermatogenesis is pertinent to its use in impotence but cannot be answered conclusively as yet. Spermatogenesis is not stimulated in immature rats by androsterone (16) or by testosterone (17). After a mature, functioning testis has been obtained, however, it is possible to maintain spermatogenesis in the hypophysectomized rodent by androgens (18, 3, 4, 19), crude progestin (19) and yeast extract (19). The mechanism of such maintenance is not clear. It has been shown (4) and confirmed (22) that male hormonal substance tends to prevent degeneration of the scrotum and ascent of the testes which follow hypophysectomy. This is believed by the author (4) to be partially responsible for maintenance of spermatogenesis. Others (22) have interpreted this mechanism as sufficient to account for the continuance of spermatogenesis entirely independent of any direct hormonal stimulation. Such interpretation of the scrotal condition as the sole factor does not appear to be correct, however, for male sex-substances have a direct effect on the testis entirely apart from an indirect one exerted through the scrotum, as seen in the changes (heavier weight and greater necrosis) produced by male substances upon cryptorchid testes of hypophysectomized rats (17). The influence of androgens upon testes placed in the abdomen cannot be explained as due to scrotal changes. So in the rat there may be direct as well as indirect (scrotal) effect of androgens on tubular tissue. Comparison of the effects in rodents with those obtained in humans is not possible at present, so it is important to examine testicular function in patients preliminary to and then following treatment with male hormone. Brosius and Schaefer (20) claim spermatogenesis produced by pregnancy urine extracts in a human whose testes were atrophied following orchitis, but there was sperm production before the illness. Further, those workers support their contention by citing spermatogenesis following the use of extract of the anterior pituitary (21), which is entirely different material from their pregnancy urine extracts and may well contain a gametokinetic factor. Tentatively, it seems in the light of our present data that neither anterior pituitary-like nor male substances should be expected to initiate spermatogenesis, but that, at least in the rodent, spermatogenesis which is already established may be maintained at least temporarily by male hormone substances.

SUMMARY

Male hormone substances produce growth, maintenance and function of the male reproductive tract. Function includes erectile ability.

Immature animals were given injections of male hormone substances, testosterone acetate and testosterone propionate, which stimulated penile growth and erection. Castration and hypophysectomy of adult rodents ap-

peared to result in regressive changes of the penis and diminution of erectile properties. Administration of male hormone to castrated and hypophysectomized male rodents resulted in the maintenance of erectile capacity.

Injections of testosterone propionate in 5 immature children, in one 27-year-old hypopituitary man, and in one 43-year-old man who had complete impotence of 8 years' duration, resulted in the production of erections, which in some cases approached a state of priapism. In immature animals, in the young children and in the hypopituitary patient the complicating influence of bodily produced male hormone and mental factors were greatly minimized, so that with additional precautions of alternating periods of injecting male substances with periods of injecting bland solutions, the stimulation of penile erections was traced directly to the presence of male hormone substances.

The clear-cut stimulation of erections in controlled cases of animals, children, and older men suggest a possible value of male hormone substances in impotence, particularly in cases of hypogenitalism. Discussion is given of the substances available, the cautions to be employed and the influence of androgenic substances upon spermatogenesis.

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TESTOSTERONE AND TESTOSTERONE ACETATE AND THE PROTEIN AND ENERGY METABOLISM OF CASTRATE DOGS[1]

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The results obtained from the study of two androgenic preparations on the protein and energy metabolism of castrate dogs have already been reported. The first report (1) was concerned with the effects of urinary androgenic extracts and the second (2) with the synthetically prepared androgen, androstenedione. In both cases there was nitrogen retention, subsequent to the injection of the androgenic material and no effect on the energy metabolism. Since testosterone has been demonstrated to be the active substance produced by the testes and is the most active naturally occurring androgenic substance known, it was necessary for the completeness of our program to note the effects of this substance. In the meantime, moreover, it has been demonstrated (3, 4, 5) that certain esters of testosterone are much more active than testosterone alone. One of the most active of these esters is testosterone acetate and since this was available in pure crystalline form, this compound also was studied.

Materials. The testosterone was provided in crystalline form[2] and was dissolved in olive oil so that 1 cc. of solution contained 5 mg. The testosterone acetate was provided in ampules containing 5 mg. per cc. and was used as such.[3] All injections were made subcutaneously and with the usual asepsis.

Animals and Diet. The 2 castrate dogs used and described in the previous reports (1, 2) were employed. They were placed on the diet given in table 1.

Procedure. As in the previous studies, the dogs were confined in metal metabolism cages and fed the prescribed diet at 5:30 P.M. Urine collections were made under toluene. Two-day periods were obtained by catheterization just before feeding on the second day.

Methods. The study of the protein metabolism was similar to that employed in the second report. We have already demonstrated clearly that the decreased protein metabolism occurs through a decrease in urea excretion, and this is the sole factor affected. Therefore, only total urinary nitrogen determinations were deemed necessary for this study. The total nitrogen content of the urine, beef heart and cracker meal was determined by the usual Kjeldahl-Gunning method.

[1] This investigation was aided by a grant from the Committee on Scientific Research of the American Medical Association.
[2] Supplied by the Schering Corporation through the courtesy of Drs. E. Schwenk and G. Stragnell.
[3] Supplied by the Ciba Company through the courtesy of Dr. C. C. Haskell.
We are grateful to the above for their generous contribution of these valuable materials.

The energy metabolism of *dog 1* was determined by use of the new automatic calorimeter developed in this department (6). Although both direct and indirect heat determinations were made, only the indirect values are reported. The direct heat determinations were unreliable because this part of the apparatus was being refined during the course of these experiments. The indirect heat determinations were checked by carrying out a series of basal determinations on the dog by means of the Benedict closed-circuit apparatus which had been used in the two previous studies. These values are indicated in table 4 and are in agreement with the values obtained by the automatic apparatus.

The energy metabolism of *dog 2* was determined by the Tissot-Haldane method employing the special helmet which was described earlier (2).

RESULTS

Protein Metabolism. In table 2 are compiled the results obtained on *dogs 1* and *2* with testosterone and testosterone acetate. Figure 1 (*dog 1*) and

TABLE 1. DAILY DIET

	Dog 1, 14.3 kg.			*Dog* 2, 25 ± 0.5 kg.		
	Gm.	Gm. N.	Calories	Gm.	Gm. N.	Calories
Beef heart	175	5.36[1]	434	225	6.88[1]	563
Cracker meal	60	1.20	233	80	1.60	322
Lard	30		270	40		360
Cod liver oil	5		45	5		45
Bone ash	10			10		
Wesson's salt mix	3			3		
		6.56	982		8.48	1290

[1] Varied with each lot of beef heart.

figure 2 (*dog 2*) are graphical presentations of these data. It is to be noted that nitrogen retention occurred after injections in each experiment. The amount retained in the experiment with *dog 1*, in which three 15 mg. injections of testosterone were administered, was rather small and was probably due to the fact that the amount of hormone was not sufficient to produce the maximum effect. Comparison of the other experiments shows no marked difference between the action of testosterone and testosterone acetate and the results agree with those of the two previous reports. The acetate possibly prolonged the period of nitrogen retention 24 to 48 hours over that demonstrated by testosterone.

The ability to prolong the effect of testosterone through esterification is more clearly demonstrated in the rat accessory sex glands (3, 4, 5) and the capon's comb (4). The results obtained here are similar to the effect on the capon's comb. There was no increase in maximum effect but there was a greater total effect due to prolongation of the maximum. In the rat test there was an increased maximum as well as a prolongation effect on the weight of the accessory sex organs.

The subsequent results are similar to those obtained with testosterone.

TABLE 2. NITROGEN METABOLISM

Dog 1		*Dog 2*	
Date N. Intake	Urinary N	Date N. Intake	Urinary N
1937		1937	
2/1 6.56 gm.	3.92	2/1 8.48 gm.	6.38
2/3	3.92	2/3	6.45
2/5	4.08	2/4 20 mg. testosterone	
2/7	3.94	2/5 20 mg. testosterone	6.42
2/9	3.94	2/6 20 mg. testosterone	
2/10 15 mg. testosterone		2/7	5.61
2/11 15 mg. testosterone	3.89	2/9	5.92
2/12 15 mg. testosterone		2/11	6.61
2/13 6.68 gm.	lost	2/13 8.64 gm.	6.85
2/15	3.74	2/15	7.25
2/17	3.70	2/17	7.19
2/19	lost	2/19	lost
2/21	3.90	2/21	7.32
2/23	3.89	2/23	7.31
		3/1 20 mg. testosterone acetate	7.25
3/3 6.59 gm.	3.62	3/2 20 mg. testosterone acetate	
3/4 25 mg. testosterone acetate		3/3 19.5 mg. testosterone acetate	6.90
3/5 25 mg. testosterone acetate	3.89	3/5	6.33
3/6 25 mg. testosterone acetate		3/7	6.32
3/7	3.72	3/9	7.57
3/9	3.54	3/14[2]	7.20
3/11	3.09	3/16	7.62
3/14[1]	3.79	3/18	7.71
3/16	4.26		
3/18	4.03		

[1] This was a 3-day period.
[2] This was a 5-day period.

There was a sudden and large increase in nitrogen excretion after the period of nitrogen retention. This same effect was noted with the two previous androgenic preparations.

Although the maximum daily nitrogen retention for *dog 1* was small in the case of the testosterone experiments, the acetate yielded data similar to

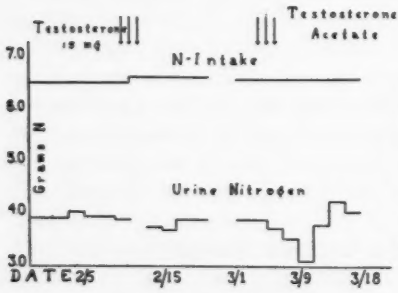

Fig. 1. Nitrogen metabolism, *Dog 1*.

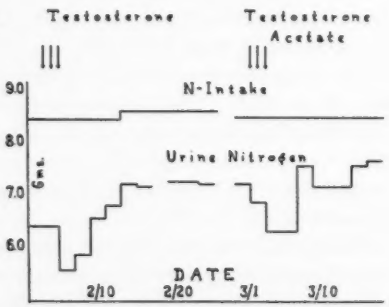

Fig. 2. Nitrogen metabolism, *Dog 2*.

those obtained with the urinary extracts and androstenedione. There was a maximum daily nitrogen retention of 0.8 gm. or 0.06 gm. per kg. per day.

The results for *dog 2* are more difficult to interpret with respect to maximum daily retention of nitrogen. After each series of experiments the basal

TABLE 3. SUMMARY OF ENERGY METABOLISM. *Dog 2*
Weight 25.0±0.5 kg. Length 90 cm. Surface area 0.84 sq. m.

Date	Time end of period	Room temp. °C.	Observed R.Q.	Calories per hr.	Calories per sq. m per hr.	Ventilation Rate liters/hr.	Respiration
1937							
1/29–2/3[1]	9:31–4:26	25.1±1.2	.73±.01	21.9±1.0	26.3±1.2	158.5±18.2	15±1
2/4	8:43	24.5	.72	21.9	26.1	157.6	16
	8:45 *Injected subcutaneously 20 mg. testosterone*						
	10:58	25.5	.78	23.0	27.3	168.2	16
	2:11	26.2	.72	22.7	27.0	148.2	14
	4:45	26.8	.76	22.6	26.9	168.2	13
		(26.1±0.5)	(.75±.02)	(22.8±0.3)	(27.1±0.2)	(161.5±8.9)	(14±1)
2/5	9:23	24.9	.72	21.9	26.1	165.2	14
	9:25 *Injected subcutaneously 20 mg. testosterone*						
	1:33	26.6	.73	23.1	27.5	161.7	13
	4:37	25.8	.73	19.4	23.1	145.3	14
		(26.2±1.4)	(.73±.00)	(21.3±1.6)	(25.7±1.8)	(158.5±13.2)	(14±1)
2/6	9:19	24.3	.72	22.4	26.6	162.4	14
	9:23 *Injected subcutaneously 20 mg. testosterone*						
	11:23	24.4	.73	23.5	27.9	170.7	15
	2:11	24.6	.73	20.6	24.5	145.7	14
		(24.5±0.1)	(.73±.00)	(22.0±1.5)	(26.2±1.7)	(158.2±12.5)	(14±)
2/9–2/15[2]	10:22–3:17	24.2±0.8	.73±.01	22.0±0.6	26.2±0.7	156.7±3.7	15±1
2/24–2/27[3]	9:39–11:27	22.1±0.7	.74±.02	21.9±0.6	26.0±0.8	158.9±13.6	15±1
3/1	9:40	20.9	.78	21.9	26.0	156.1	15
	9:43 *Injected subcutaneously 20 mg. testosterone acetate*						
	12:18	23.2	.76	22.0	26.1	146.1	12
	2:50	23.9	.74	21.8	26.0	147.2	14
	5:07	24.4	.75	21.5	25.6	149.1	
		(23.8±0.4)	(.75±.01)	(21.8±0.2)	(25.9±0.2)	(147.4±1.1)	(13±1)
3/2	8:50 *Injected subcutaneously 20 mg. testosterone acetate*						
	10:18	24.2	.73	21.7	25.8	154.2	14
	1:48	25.6	.74	23.2	27.6	163.5	16
	3:30	25.4	.74	22.3	26.5	158.3	14
		(25.1±0.6)	(.74±.00)	(22.4±0.5)	(26.6±0.6)	(158.6±3.2)	(15±1)
3/3	9:00 *Injected subcutaneously 19.5 mg. testosterone acetate*						
	10:48	26.1	.71	21.3	25.4	158.4	17
	1:50	26.3	.72	22.0	26.2	159.7	17
	5:04	26.7	.71	19.9	23.7	146.9	17
		(26.4±0.2)	(.71±0.0)	(21.1±0.7)	(25.1±0.9)	(155.0±5.4)	(17)
3/6	3:21	25.4	.73	21.5	25.6	151.6	17
3/9	11:10	23.8	.76	21.8	26.0	157.1	17

[1] Average of 11 determinations.
[2] Average of 4 determinations.
[3] Average of 5 determinations.

figures for urinary nitrogen increased. This is especially true in the testosterone experiments. Here the dog was in equilibrium at 6.38 to 6.45 gm. urinary nitrogen per day and after the experiment, it maintained a balance at a level of 7.2 to 7.3 gm. urinary nitrogen per day. Therefore, on the basis of the preliminary basal period, the maximum daily nitrogen retention amounts to only 0.8 to 0.9 gm. while on the basis of the after period it amounts to 1.5 gm., after deducting the increase due to increased nitrogen intake. In the second series of experiments the differences are not so great but are evident. On the basis of the preliminary basal values for this experiment, there was a retention of 1.0 gm. per day. This is similar to that obtained in the testosterone experiments. Again we find an increase in the after basal periods, though not so great as in the previous case.

These differences do not alter the main results of the experiments. There

was always nitrogen retention as a result of the injection of androgenic substances. This effect is presented solely because of its metabolic value and not as a final quantitative fact. The result could be used in a semiquantitative manner but the nature of the experiment would not make it feasible for practical purposes.

Energy Metabolism. The results obtained on the two dogs were similar. There was no marked effect on energy metabolism, R.Q., ventilation rate or

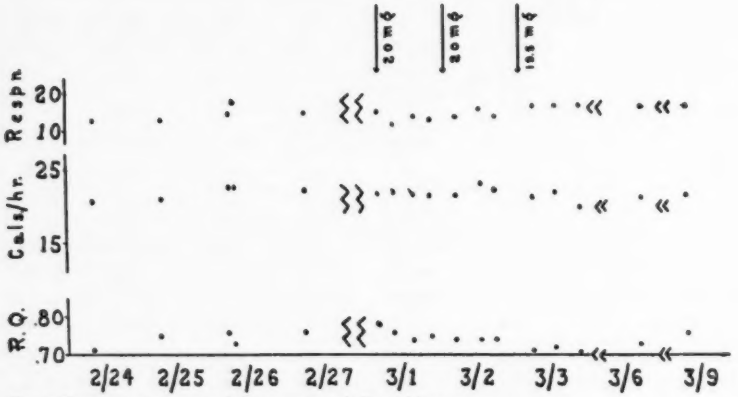

Fig. 3. Testosterone acetate and the energy metabolism of *Dog* 2.

respiration. The last two observations were obtainable only on *dog 2* because of the nature of the apparatus used for *dog 1*.

The data for *dog 2* are presented in detail in table 3 and results of one series of experiments are presented graphically (fig. 3) in order to depict

TABLE 4. SUMMARY OF ENERGY METABOLISM, *Dog.* 1
Length 80 cm. Wgt. 14.3 kg. S.A.=.606 sq. m.

Date	Duration of determination	Observed R.Q.	Calories per hr.	Calories per sq. m. per hr.
1/30–2/1[1]		.74	16.0	26.4
2/10	*Injected 15 mg. testosterone at 9:45*			
	1:41–5:16	.77	15.4	25.4
2/11	*Injected 15 mg. testosterone at 8:40*			
	10:59–2:20	.77	15.3	25.2
2/12	*Injected 15 mg. testosterone at 8:55*			
	1:55–5:25	.79	16.9	27.9
3/2	11:57–3:46	.78	16.0	26.4
3/3	12:03–3:34	.79	15.4	25.4
3/4	*Injected 25 mg. testosterone acetate at 9:40*			
	1:25–4:25	.73	16.4	27.1
3/5	*Injected 25 mg. testosterone acetate at 8:50*			
	1:30–4:30	.77	16.1	26.6
3/6	*Injected 25 mg. testosterone acetate at 9:30*			
	11:00–2:00	.79	15.9	26.3
3/10	1:44–5:11	.75	15.4	25.4
3/11	1:25–4:37	.74	15.8	26.1
3/12	1:45–4:58	.77	15.8	26.1

[1] These values were obtained by the use of the Benedict Universal closed circuit apparatus. Each entry represents the average of 3 to 4 hourly periods.

all variations and hourly as well as daily agreements in results. The results for *dog 1* (table 4) are condensed to daily values since they are the results of determinations obtained in 3 to 4-hour periods.

The inability of testosterone or testosterone acetate to affect the energy metabolism of these dogs is in complete confirmation of the results obtained with the two other androgenic preparations of different chemical structure. Furthermore, the as yet unpublished results (7) being obtained in Koch's laboratory, and referred to in his review, confirm our data.

In our last report (2) we mentioned that urinary extracts had no effect on the energy metabolism of human subjects. Since then, similar results have been found with the use of testosterone and testosterone acetate even after daily administration for several weeks.

DISCUSSION

We have completed a study of the effects of naturally occurring androgens, a purely synthetic product, androstenedione and an activated natural product, testosterone acetate, on the protein and energy metabolism of castrate dogs. In no instance have we been able to detect any effect on the basal metabolism that would indicate that these substances are calorigenic agents. The question of sufficiency of material injected was fortunately controlled by the observation that although no calorigenic effects could be detected with the doses used, there was a marked effect on the protein metabolism which could be readily measured.

Since androgenic material is now readily available for clinical use, it is appropriate that further investigation and confirmation of this question be made on human subjects by clinicians.

SUMMARY

Testosterone and testosterone acetate cause a retention of nitrogen but do not affect the energy metabolism of castrate dogs. The results in both cases are similar to those obtained in previous studies with urinary male hormone extracts and androstenedione.

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THE EFFECT OF TESTOSTERONE, TESTOSTERONE PROPIONATE AND DEHYDROANDROSTERONE ON THE SECRETION OF THE GONADOTROPIC COMPLEX AS EVIDENCED IN PARABIOTIC RATS[1]

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A number of experimental studies have indicated that androgenic preparations are able to limit the secretion of gonadotropic complex by the anterior pituitary. Martins and Rocha (1) were able to prevent ovarian stimulation of female rats in parabiosis with castrated male rats by subcutaneous implantation of fresh, macerated rat testicle into the castrated males, but not in females joined to castrated females which had also received testis tissue. These investigators concluded that they had demonstrated a sex-specific suppression of hypophyseal gonadotropic secretion. McCullagh and Walsh (2) also observed that the hypertrophy of the male accessory organs which usually occurs when an adult male rat is placed in parabiosis with a castrate partner can be prevented by the administration of both the fat-soluble and fat-insoluble fractions of beef testes to the castrate partner. Nelson and Gallagher (3) have reported that androsterone, androstanediol, and androstenedione will prevent the development of castration changes in the pituitary of the spayed virgin female rat. Wolfe and Hamilton (4) have shown that testosterone, testosterone acetate, and testosterone propionate similarly prevent the development of the typical castrate morphology in the gonadectomized male or female rat. Schoeller, Dohrn, and Hohlweg (5) have also reported that testosterone propionate, testosterone, and androsterone prevent the development of castration changes in the pituitaries of both male and female rats. Moore and Price (6), employing immature female mice as test animals, have shown that androsterone can effect a reduced gonadotropic potency in the rat pituitary as well as extensive testicular damage.

Meyer and Hertz (7) have recently presented data indicating that the ovarian hypertrophy which obtains when an immature female rat is put into parabiosis with a castrated male or female litter-mate may be regarded as a quantitative measure of the level of gonadotropic secretion produced by the pituitary of the castrated partner. We have accordingly employed such criteria in the present study of the effect of testosterone, testosterone propionate, and dehydroandrosterone on the gonadotropic activity of the pituitary of the castrated male and female rat.

[1] Supported in part by a Grant from the Wisconsin Alumni Research Foundation administered by Roland K. Meyer.
[2] Chappel Bros. Fellow in Endocrinology.

MATERIAL AND METHODS

This study includes observations upon a total of 114 pairs, including 23 untreated control pairs and 91 experimental pairs treated with varying doses of testosterone propionate, testosterone, and dehydroandrosterone.[3] These respective compounds were selected to represent substances of high, medium, and low androgenic effectiveness (8). In addition we wish to present a summary of all of our data on untreated control pairs obtained during the past year. This includes 44 castrate male-female pairs and 41 castrate female-female pairs.

The operative procedure used in uniting the animals was that described by Bunster and Meyer (9) except that metal skin clips were used for closing the skin wounds instead of silk sutures. The operations were conducted under sterile conditions and under ether anaesthesia. By adequate post-operative care the mortality was maintained at 5 per cent.

In all cases litter-mates were employed. All of the animals were united at from 30 to 33 days of age, and one partner was gonadectomized at the same time. Injection of androgenic substances into the gonadectomized partner was begun within 3 hours of the time of operation and was repeated daily for 10 days. All injections were given subcutaneously in 0.05 cc. of corn oil. It was necessary to warm the oil gently in order to dissolve the relatively large quantities of dehydroandrosterone. All animals were autopsied on the morning of the 11th day of parabiosis. At the time of autopsy the ovaries of the normal female partners were dissected free and weighed to the nearest milligram. Observations were made upon the gross qualitative condition of the ovary, the size of the uterus, and the time of vaginal opening.

The quantity of androgen administered daily, the mean ovarian weight and distribution of ovarian weights in each series, the mean seminal vesicle weight of the gonadectomized male partner, etc., are to be found in table 1. The data are unselected and include our findings in all animals surviving the experimental procedures, except for two pairs which were in such poor condition as to make it doubtful that their responses were normal.

RESULTS AND DISCUSSIONS

In our preceding study (7) we have emphasized the quantitative limitations of the parabiotic method and have pointed out the necessity for adequate statistical analysis of a substantial body of data. Employing Fischer's formula for small numbers (10), we have determined the statistical significance of the difference between each experimental series and its respective control group and between certain experimental series. Since our experimental data apparently present a skewed distribution, we appreciate that the mean and standard error of each group may not adequately describe the data. We have, therefore, also presented the actual distribution by classes of the ovarian weights of experimental and control pairs.

[3] We wish to thank Dr. Erwin Schwenk of the Schering Corp. for the supply of testosterone and testosterone propionate used in this work. We are also indebted to Dr. W. H. McShan and Dr. M. A. Spielman for preparing the dehydroandrosterone.

Control series I represents the untreated control pairs which were actually run simultaneously with the androgen-treated pairs. Control series II, III, and IV are constituted of untreated control pairs observed in conjunction with other experimental studies throughout the past year. The essential agreement between the findings in the three respective control series indicates the readiness with which such data are repeatedly obtained. The distribution of the ovarian weights by classes, however, shows the range of variability which occurs even under constant conditions. Thus, of the total of 85 control pairs, 11 or 13 per cent showed no ovarian stimulation. We are unable to account

TABLE 1

Androgen	Sex	Dose[1]	Total No. of Pairs in Group	Mean Ovarian Wt. ± S.E.	Mean Seminal Vesicle Wt. ± S.E.	Ovarian Wt. Distribution (mg.)[2]					
						-20	21-34	35-54	55-94	95-144	145-224
Testosterone	♂♀	10	10	68.6± 13.7	12.1± .79	2	2	—	4	2	—
	♀♀	10	14	19.2± 4.3	—	12	—	1	1	—	—
	♂♀	30	9	29.1± 6.8	16.8±1.04	5	2	1	1	—	—
	♀♀	30	9	16.0± 1.2	—	8	1	—	—	—	—
	♂♀	50	8	24.6± 4.2	23.0±2.51	4	2	2			
	♂♀	75	8	14.7± .90	17.3±1.14	8	—	—	—	—	—
	♂♀	100	6	20.1± .95	20.0±1.76	4	2	—	—	—	—
Testosterone propionate	♂♀	2	5	104.8± 5.19	13.6± .7	—	—	—	1	4	—
	♂♀	10	5	52.4±23.2	35.0±2.6	2	1	—	1	1	—
	♂♀	15	5	18.8± 1.07	49.8±5.09	4	1	—	—	—	—
Dehydro-androsterone	♂♀	1000	5	56.4±13.82	9.4± .17	1	—	2	2	—	—
	♂♀	3000	7	15.2± 1.25	52.8±5.9	6	1	—	—	—	—
Control (I)	♂♀	0	13	123.8±17.9	8.57± .52	2	0	0	2	3	6
	♀♀	0	10	67.0±13.03	—	1	1	3	2	2	1
Control (II)	♂♀	0	16	72.8±13.52	—	4	1	3	3	4	1
	♀♀	0	11	71.0±12.3	—	1	2	1	4	3	1
Control (III)	♂♀	0	7	89.2±15.87	—	1	—	1	—	5	—
	♀♀	0	5	81.8±18.27	—	1	—	—	1	3	—
Control (IV)	♂♀	0	8	81.2±13.19	—	1	—	—	6	—	1
	♀♀	0	15	90.06±11.61	—	—	1	3	5	5	1
Combined Control	♂♀	0	44	92.09± 8.42	—	8	1	4	11	12	8
	♀♀	0	41	78.31± 6.55	—	3	4	7	12	13	2

[1] Daily dose, in gamma, administered subcutaneously in 0.05 cc. corn oil.
[2] The ovarian weights of 6 normal rats of similar age and body weight were found to be: 14, 16, 18, 19, 20, and 21 mg. respectively, the mean being 18±1.13 mg.

for the lack of response in these cases since they were indistinguishable from other control pairs in rate of healing and absence of infection. In the combined control group, 58 pairs or 68.4 per cent attained ovarian weights of 55 mg. or more, and 69 pairs or 81.3 per cent of the total number had ovaries exceeding 35 mg. in weight. In each control series and in the combined control series the ovarian weights obtained in castrate male-female pairs are not statistically significantly different from those obtained in castrate female-female pairs. We feel that this body of data on untreated pairs affords an adequate control for our experimental observations.

The data indicate that all of the androgens employed have the capacity to completely suppress the gonadotropic secretion of the pituitary. Moreover, the degree of inhibition is roughtly proportional to the dosage administered. Thus we find that whereas a daily dose of 10γ of testosterone reduces the mean ovarian weight in castrated male-female pairs to 68.6 ± 13.7 mg., 30γ brings

the mean ovarian weight down to 29.1 ± 6.8 mg. and 75γ reduces the ovaries to the immature level of 14.7 ± .90 mg. Similar data are found in the case of dehydroandrosterone and testosterone propionate. It is thus apparent that these substances are able to quantitatively check the hypersecretion of gonadotropic complex which normally follows gonadectomy.

The data also give some evidence concerning the relative efficiency of these three androgens in limiting the secretion of gonadotropic substances by the pituitary. A comparison of absolute dosages on a weight-for-weight basis indicates that the respective inhibitory capacities of the compounds are in the same relationship as their androgenic effectiveness. Thus we see that for the degree of inhibition in castrated male-female pairs which can be obtained with as little as 15γ of testosterone propionate one requires more than 30γ of testosterone and more than 1,000γ of dehydroandrosterone. We have not determined the minimal effective dosage of each substance with sufficient precision to warrant very close comparisons. It is clear, however, that a direct relationship exists between the androgenic potencies of the compounds studied and their ability to effect pituitary inhibition.

There seems, however, to be no relationship between the minimal pituitary inhibitory doses of the three androgens investigated and the respective effects of such doses on the weight of the seminal vesicles of the gonadectomized partner. Thus, 10γ daily of testosterone proportionate produced a mean seminal vesicle weight of 35.0 ± 2.6 mg. and reduced the mean ovarian weight to only 52.4 ± 23.2 mg., whereas 30γ daily of testosterone reduced the mean ovarian weight to 29.1 ± 6.8 mg. and gave a mean seminal vesicle weight of only 16.8 ± 1.04. It is not feasible to refer our findings on the androgenic effects of these substances to the assay curves offered by Tschopp (11) and Deanesly and Parkes (12) since our procedures differ so widely from theirs with regard to age of test animals, length of castration and volume of oil administered. Nevertheless, our own conditions have been constant and therefore warrant comparison between our experimental groups. Such comparisons make it clear that the weight of seminal vesicle produced by a given androgenic treatment is not an adequate index of the degree of hypophyseal suppression which such treatment will bring about.

The findings in castrate female-female pairs as compared with those in castrate male-female pairs indicate that the castrate female pituitary is completely suppressed by a quantity of testosterone which is only partially effective upon the castrate male gland. Comparing our series of 14 female-female pairs given 10γ of testosterone daily with the group of 10 castrate male-female pairs given the same treatment, we find a mean ovarian weight of 19.2 ± 4.3 mg. in the former and a corresponding weight of 68.6 ± 13.7 mg. in the latter. The difference between these two groups is statistically highly significant, and indicates the greater potency of the male glands. Nevertheless, the difference between the castrate male-female control pairs and the castrate female-female pairs is not statistically significant. These findings are in agreement with our results in similar experiments with estrone (7) and with the

earlier morphological data of Hohlweg and Dohrn (13) relating to the greater requirement of estrone for the prevention of castration changes in the pituitaries of male rats as compared to females. We may conclude that the gland of the castrated female as well as the castrated male pituitary can be suppressed by testosterone, and that the latter requires a substantially larger quantity for complete inhibition.

The hypertrophied ovaries of the control and experimental pairs showed no qualitative differences. When stimulated, the ovaries were practically always composed of large follicles and corpora lutea with the corpora predominating.

We wish to further emphasize the adaptability of the parabiotic method for quantitative studies on the gonadotropic secretion from the anterior pituitary. It affords a means of studying quantitatively the output of the gland in situ during a given period of time.

It is at present difficult to evaluate the significance of the suppression of the pituitary by androgenic materials for the normal physiology of the male individual. One should, however, appreciate the greater efficiency of estrone in limiting the gonadotropic activity of the pituitary. Our studies indicate that as little as 0.2γ of estrone daily will inhibit the male pituitary as effectively as a daily dose of 30γ of testosterone or 15γ of testosterone propionate (7). This greater inhibitory efficiency of estrone is supplemented by the initially lower potency of the female pituitary. These factors suggest that the pituitary-gonadal interrelationship of the female is more delicately regulated than is that of the male.

SUMMARY AND CONCLUSIONS

The ovarian hypertrophy which obtains when an immature female rat is put into parabiosis with a castrated male or female litter-mate is employed as a quantitative measure of the level of hypophyseal gonadotropic secretion.

Data are presented from observations on 114 pairs including 23 untreated control pairs and 91 pairs in which the gonadectomized partner was treated with varying doses of testosterone, testosterone propionate, and dehydroandrosterone. In addition, there are given the control data obtained from a combined series of all untreated pairs observed in association with other experimental studies. This includes 41 castrate female-female pairs and 44 castrate male-female pairs.

It is concluded from the data that: 1). The administration of adequate doses of testosterone propionate, testosterone, and dehydroandrosterone to the castrated partner completely inhibits the ovarian hypertrophy usually observed in the normal partner, and the degree of ovarian hypertrophy progressively increases as the dose of androgen is reduced; 2). Larger doses of testosterone are required for inhibition in castrate male-female pairs than in castrate female-female pairs; 3). On a weight-for-weight basis, the relative capacity of these three androgens to inhibit pituitary gonadotropic secretion is in the same order as their respective androgenic potencies, testosterone propionate being most effective and dehydroandrosterone least effective. Nevertheless, equally inhibitory dosages of the three respective androgens do not produce comparable seminal vesicle weights.

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PLASMA ELECTROLYTE DISTURBANCE IN PATIENT WITH HYPERCORTICOADRENAL SYNDROME CONTRASTED WITH THAT FOUND IN ADDISON'S DISEASE[1]

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During the past few years it has been demonstrated, chiefly by the work of Bauman (1), Loeb (2), Harrop (3) and their associates, that the suprarenal glands play an important role in the regulation of the base metabolism of the body. Bauman and Kurland in 1926 found the plasma sodium and chloride to be decreased and the potassium, magnesium and calcium to be increased in cats and rabbits as a result of suprarenalectomy. In 1932 Loeb discovered the sodium and chloride of the blood plasma to be significantly decreased and the potassium to be increased in untreated cases of Addison's disease. Furthermore, he found such patients to be benefited greatly by the ingestion of sodium chloride in relatively large amounts. He and his associates (4) later reported similar findings in experimental adrenal insufficiency in dogs. They showed the lowering of the plasma sodium and chloride to be due to increased excretion of these elements. At the same time potassium appeared to be released from the cells of the body into the plasma at an abnormally rapid rate or to be retained as a result of impaired renal function. Harrop and his associates, working independently, observed similar changes in the chloride, sodium and potassium of the blood serum of adrenalectomized dogs and reported slight increases in the calcium and magnesium as well. They also confirmed the observation of Loeb regarding the beneficial effects of sodium chloride administration in Addison's disease. As a corollary to this latter finding, they pointed out that salt restriction accentuates the symptoms of adrenal cortical insufficiency and so may be employed as a reliable diagnostic test in latent cases of Addison's disease.

Various workers have found that suprarenalectomized animals, while greatly benefited by sodium chloride, cannot be made to survive indefinitely by the aid of this salt alone without the administration of potent cortical extract. When it is given as the only source of sodium the latter is excreted more rapidly than chloride, which results in the development of acidosis with a marked reduction in the plasma bicarbonate. Harrop and his co-workers (5) were able to avoid this effect and hence to maintain suprarenalectomized dogs in apparently normal condition over periods of many months by giving part of the extra sodium administered as sodium bicarbonate without use of cortical extract. Allers and Kendall (6) confirmed this result by using sodium citrate

[1] Study aided by Grant from the Medical Graduate Research Fund of the University of Minnesota.

or sodium bicarbonate along with sodium chloride. These latter workers (7) have added the interesting observation that far less sodium is required for maintenance of such animals if the potassium content of the diet is made extremely low. Hastings and Compere (8) and Zwemer and Truszkowski (9) have likewise stressed the importance of potassium, pointing out the similarity between the symptoms of poisoning by this element and those of corticoadrenal insufficiency.

Up to the present time little attention has been given to the possibility that hyperfunction of the adrenal cortex might give rise to a disturbance in the electrolyte balance of the body quite different from that which is now recognized as being characteristic of adrenal insufficiency. The present report deals with a case, answering the clinical description of 'suprarenal cortical syndrome' or 'pituitary basophilism' of Cushing, in which the plasma electrolyte pattern showed abnormalities which were in most respects diametrically opposite those found in Addison's disease. A review of the literature revealed but one other case similar to this, namely, case 2 in the series reported briefly by Walters, Wilder and Kepler (10). While the disturbance was less marked in their patient, she showed a persistent tendency toward a high plasma CO_2 combining power (79 to 87 vol. per cent) with reduction in the chlorides, sodium, potassium, total base, calcium and phosphorus. These values, like the clinical condition of the patient, tended to return to normal following partial resection of the hyperplastic adrenals, which suggests that the disturbance in acid-base balance was due specifically to overactivity of these glands.

REVIEW OF CLINICAL DATA IN PRESENT CASE

The clinical features of the present case have already been reported in brief by Ulrich (11). For the sake of convenience to the reader, however, the essential details regarding the patient will be repeated here.

M. V., a married woman, aged 44 years, was admitted to the University of Minnesota Hospital on February 11, 1935 complaining chiefly of excessive general weakness and a feeling of numbness in the extremities. At times she suffered from dyspnea and edema of the ankles. So far as could be ascertained, her present illness dated from about January 1934, at which time she first became aware of an appearance of puffiness and flushing of her face and neck with a noticeable increase in body weight. This was soon followed by an increasing growth of coarse hair over the chin, cheeks and upper lip, which required the use of some form of hair remover every few days. In April of the same year she complained of pain in the back, increased thirst, nycturia, and headache. At that time during a short stay in the hospital her family physician discovered that her systolic blood pressure was elevated to 220 mm. Hg and that she was suffering from glycosuria. The latter was partially controlled by a change in diet and occasional injections of insulin given by the physician. In July she ceased to menstruate and suffered more frequently than previously from hot and cold flashes, sweating and vague pains or numbness in her legs. In spite of a right ovariectomy in 1922 when her appendix was removed, her menstrual periods had been regular up to this time. No insulin was given between July and October. During this interval she continued her regular household work in spite of weakness, polydipsia and polyuria. Between October and December she was given 15 U of insulin twice daily with some improvement in her condition.

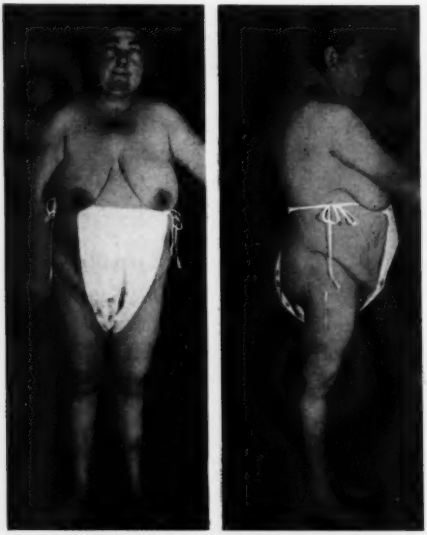

Fig. 1. Patient M.V. Front and side views, to show peculiar distribution of adipose tissue and striae atrophicae.

Fig. 2. Patient M.V. Front and side views of face to show suffusion and hirsutism of face and exophthalmos.

No more insulin was given until after her admission to the University Hospital in February 1935. At this time she complained of muscular weakness, impaired vision and taste, swelling of legs, shortness of breath, pains in knees and various vasomotor disturbances such as hot and cold flashes.

Physical Examination. The patient was obviously very weak and preferred to remain seated or in bed most of the time. Her mouth was dry and the speech was slow, somewhat slurring and monotonous. She was obviously obese about the torso, face and neck while the extremities were thin. The hands and feet were suffused or cyanotic. The skin over the abdomen, thighs and breasts showed recently developed

purplish striae. In spite of a moderate degree of exophthalmus, her eyes were expressionless and the sclerae were injected. The face was dull, puffy and ruddy to purplish in color. Coarse, dark hair was scattered profusely over the upper lip, chin and sides of her face. These features are illustrated in the photographs in figures 1 and 2. Slight pitting edema over the tibiae and a moderate increase in the area of cardiac dullness could be made out. The blood pressure, measured at various times throughout her 104 days in the hospital, varied between 140 and 210 mm. Hg systolic and 92 and 130 diastolic. The eyegrounds showed moderate arterial hypertensive changes. The visual fields were normal. The thyroid gland was not palpable. The lungs were clear. No masses could be felt in the abdomen. Deep reflexes were present but sluggish. X-ray examination of the skull showed the sella turcica to be normal in size. Rarefaction of the long bones and vertebrae was not conspicuous. Pyelograms showed the kidneys to be normal in size and position. The heart shadow was slightly enlarged to the left. Her height was 5 feet, 1½ inches; her weight, 192 pounds.

Laboratory studies. At the time of her admission the urine showed a faint trace of albumin, a two-plus positive test for sugar, but a negative test for diacetic acid. The phenolsulphonephthalein test showed an output of 55 per cent in 2 hours. The blood count was as follows: hemoglobin 86 per cent; white blood cells 9,300 with polymorphonuclears 89 per cent and lymphocytes 11 per cent. The fasting blood sugar was 387 mg. per 100 cc. Except for one attack of muscular spasms of the extremities, the patient had at no time had any clinical signs of alkalosis. Still, the carbon dioxide combining power of her blood plasma was 112 volumes per cent and the pH varied between 7.55 and 7.60 as determined by the glass electrode method, without previous insulin or alkali therapy. The serum non-protein nitrogen was 29 mg. and the cholesterol 327 mg. per 100 cc. The serum calcium was 8.4 mg. and the inorganic phosphorus 2.7 mg. per 100 cc. The blood Wassermann reaction was negative. Tests for gastric acidity showed the complete absence of free HCl on various occasions before treatment and after cortin and NaCl therapy as well. Because of the unusually high CO_2 combining power and pH of the plasma, special studies of the electrolyte pattern to be described below were made.

After a period of 10 weeks of essentially ineffective dietary and other therapy of various types, the patient developed bronchopneumonia and a streptococcic septicemia immediately followed extraction of an infected tooth and died on April 26, 1935.

Postmortem examination showed, in addition to the above described obesity, hirsutism, acrocyanosis and striae of the skin of long standing, recent cellulitis of the face and scalp on the right side and bilateral bronchopneumonia. The kidneys appeared normal except for a moderate degree of cloudy swelling. The heart weighed 400 gm. with some thickening but no fibrosis of the left ventricle. The liver was somewhat fatty and weighed 1900 gm. The pancreas appeared normal both grossly and microscopically. The right ovary was missing, the left appeared normal, weighing 7.4 gm. The thyroid weighed 19 gm. and showed no adenoma or hyperplasia. The parathyroids were normal in size and microscopic appearance. The adrenals appeared to be moderately enlarged. One weighed 14, the other 12.4 gm. No adenomata were found. Microscopically neither adrenal showed unmistakable evidence of hyperplasia of the cortex or medulla at the time of death, but definite evidence of chronic lymphocytic infiltration and edema which may have been sufficient to account for the moderate degree of enlargement noted. The hypophysis weighing 0.6 gm. was normal in size and gross appearance and the sella turcica

showed no erosion. Microscopically serial sections, differentially stained showed extensive hyaline changes in the basophils of the anterior lobe and to a less extent in those of the posterior lobe as described by Crooke (12). These changes have been clearly described in this and two other cases by Rasmussen (13). The pineal body was normal. The thymus was rudimentary.

STUDY OF THE PLASMA ELECTROLYTES

Because of the unexpected finding of an essentially asymptomatic alkalosis of severe grade, an extensive investigation of the plasma electrolyte pattern

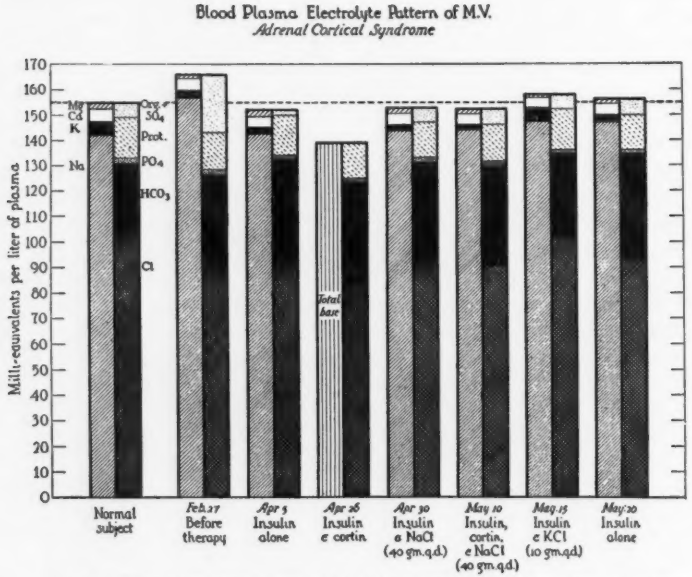

Fig. 3. Plasma electrolyte patterns of M.V. before and after various forms of therapy. Compare with normal.

was made while a variety of therapeutic procedures were tested. The results are charted in figure 3.

In comparison with the data obtained in the case of a normal subject by means of the same chemical procedures, it is obvious that the electrolyte pattern of our patient was greatly distorted, especially before any special therapy had been instituted. The most striking abnormalities as recorded for the second section of the chart (Feb. 27) were marked reduction in the concentrations of potassium and chloride and a marked increase in sodium, CO_2 content and the SO_4 plus total organic acid fraction. The latter was not determined directly but was estimated by difference, i.e., total base minus total of determined acid fractions. The serum proteins, calcium and inorganic phosphate were moderately decreased. It is seen that the patient's plasma sodium at the outset was alone greater in amount than the combined values of all of the bases in the case of the normal subject. Since ketonuria was never observed, it cannot be said what particular organic acids made up the major portion of the balance

between the total base and the determined acid, unless it is assumed that ketone acids were retained to balance the excess base. Unfortunately lactic acid and the ketone bodies of the blood were not determined.

After the patient had been for one week on a diet containing 90 gm. of carbohydrate, 30 gm. of protein and 32 gm. of fat or 770 calories, while receiving 110 U of insulin daily, the urine was sugar-free and the plasma base and acids were found to be as indicated in pattern three (April 5). It will be seen that the total base was then essentially normal except for persistence of the decrease in potassium concentration, which was less than half the normal value, and a slight reduction in the serum calcium. On the acid side the chloride remained low and HCO_3 exceptionally high. The inorganic phosphorus was unchanged, but the organic acid fraction appeared to be diminished almost to the vanishing point. On a much reduced insulin dosage and an increase in total calories to 1100, the patient thereafter continued to show freedom from glycosuria as well as ketonuria. Nevertheless, the electrolyte pattern remained abnormal, showing the basic disturbance to be essentially unrelated to the diabetes.

To determine whether cortin might accentuate the disturbance or alter the electrolyte pattern or the patient's clinical condition for the better, a potent preparation of this hormone[2] was given daily in medium sized doses. The only determinations made at this time were total base, chloride, HCO_3 and PO_4 and protein. It will be seen that the total base was diminished, the chloride lowered and the other factors essentially unchanged. The patient's clinical symptoms were likewise unchanged by this therapy.

In an attempt to raise the chloride of the plasma to normal, sodium chloride was then given by mouth to the amount of 40 gm. daily for 4 days. At the end of this time analyses showed the values presented in the fifth column (April 30). As compared with the corresponding values for the normal subject (column 1), it can be seen that the chloride and potassium both remained subnormal while the HCO_3 remained greatly increased. The sodium was normal. Administration of cortin and large doses of sodium chloride simultaneously did not change the values significantly, as shown in section 6 (May 10). The potassium was reduced to a slightly lower level only.

After discontinuance of both the cortin and sodium chloride, the administration of potassium chloride in doses of 10 gm. daily was carried out for 5 days. As recorded in the next section of the chart (May 15), the potassium and chloride were restored entirely to their normal values for the first time. At the same time the sodium, instead of being decreased as it is in the normal subject by administration of potassium, was increased slightly. In spite of this, however, the HCO_3 value was decreased by more than 20 per cent. It was thought that the patient experienced subjective improvement as a result of the potassium chloride administration. In keeping with the observations of McQuarrie, Thompson and Anderson (14), regarding the antagonistic effects of sodium and potassium salts on blood pressure, she showed a con-

[2] Cortin kindly supplied by Dr. E. C. Kendall.

TABLE 1. COMPARISON OF DATA FROM TYPICAL CASE OF ADDISON'S DISEASE WITH THOSE FROM OUR PATIENT M.V.

Data	Addison's Disease	Patient M.V.
Clinical		
Nutrition	Emaciated	Adiposity of trunk, neck and face
Skin	Pigmented	Dusky, florid face; acrocyanosis; purplish striations
Hair	Normal or sparse	Hirsutism; hypertrichosis of extremities
Eye balls	Endophthalmos	Exopthalmos
Sex function	Diminished	Diminished
Blood pressure	Reduced	Elevated
Body temperature	Subnormal	Normal
Basal metabolism	Reduced	±0% to +16%
Plasma CO_2 combining power	Decreased	Greatly increased
Gastrointestinal	Hypochlorhydria; anorexia; vomiting; diarrhea	Achlorhydria; anorexia to normal appetite
Blood volume	Reduced	Normal
Skeleton	Normal	Normal to slight osteoporosis
Voice	Normal	Masculine; rough
Postmortem		
Adrenal glands	Atrophic or necrotic	Enlarged; evidence of inflammation and edema
Pituitary	Decreased basophils in anterior lobe	Basophils of anterior lobe hyalinized
Blood Constituents		
Sugar	Hypoglycemia	Hyperglycemia (frank diabetes)
Sodium	Decreased	Increased
Potassium	Increased	Decreased
Calcium	Slightly increased	Slightly decreased
Magnesium	Increased	Decreased
Chloride	Decreased	Decreased
Bicarbonate	Decreased	Greatly increased
Inorganic phosphorus	Slightly increased	Slightly decreased
Non-protein nitrogen	Increased	Normal
Serum Proteins	Increased	Decreased
Response to Therapy		
Cortin	Beneficial	Not helpful
NaCl solution	Beneficial	Not helpful
KCl solution	Harmful	Beneficial
Insulin	Harmful	Beneficial

sistent lowering of both her systolic and diastolic levels during this potassium ingestion period and an elevation during the preceding sodium chloride period.

In order to repeat this last experiment to reassure ourselves regarding its significance, we discontinued the potassium chloride ingestion to obtain a new base line. From the last column (May 20), showing the results of analyses made 5 days after omitting the potassium chloride, it is obvious that the potassium and chloride were again reduced to subnormal levels while the HCO_3 had again increased to a value more than 50 per cent above normal. At the same time the sodium remained at a value approximately equal to the sodium plus the potassium of the normal subject.

Following the extraction of a tooth, which began to give the patient some discomfort at this time. she developed a facial cellulitis and septicemia which caused her death before the most promising of the foregoing experiments could be repeated.

COMMENT

Judging from our knowledge of the disturbances in the base metabolism, which result from adrenal insufficiency, and the similarity of the clinical picture presented by our patient and by those reported in the literature as proved cases of corticoadrenal syndrome, we believe that the unusual disturbance in the plasma electrolyte pattern reported here was due to hyperfunction of the adrenal cortex. The almost complete contrast between the abnormalities, both clinical and chemical, shown by a typical case of Addison's disease and those of our patient exhibiting what we assume to be a hypercorticoadrenal syndrome is striking, as shown in the accompanying table, summarizing comparative data. A comparison of the plasma electrolyte pattern from a severe, untreated case of Addison's disease with that from our own case of hypercorticoadrenalism before treatment was begun and that from a normal subject is presented in figure 4. It is readily seen that the pattern for the normal subject stands midway between the extremes shown by the two types of abnormality as regards every electrolyte excepting chloride. This alone is low in both types of disturbance. Its failure to increase in the case of our patient as a result of ingesting enormous amounts of sodium chloride would suggest that the abnormality involves primary retention of bicarbonate rather than secondary retention due to excessive loss of chloride. The restoration of a normal chloride value as well as a normal potassium value, following potassium chloride administration in much smaller doses, suggests that the chloride concentration was in some way conditioned by the potassium level. Since sodium is said to be more readily excreted than chloride or potassium in adrenal insufficiency, it is perhaps not unreasonable to suppose that the reverse might be the case in hyperfunction involving the same cortical principle.

In regard to the frequency of occurrence of cases such as that reported here, in which a grave disturbance of the acid-base metabolism can be demonstrated by blood analyses, it must be emphasized that they are probably extremely rare. That minor disturbances in this same direction might be discovered more frequently among cases of hypercorticoadrenalism by means of complete mineral balance studies would be our guess. The only additional case in which we have determined the plasma electrolyte distribution was that of a 13-year-old boy who showed practically all of the typical symptoms and clinical sings of the syndrome as a result of a large metastisizing carcinoma of the ardrenal cortex. In this instance, no definite alteration in the plasma electrolytes was discovered.

Regarding the pathological findings in the case of M. V., it must be admitted that any cortical hyperplasia of the adrenal that may have been present earlier in the course of her illness was more or less obscured by the time of her death by the occurrence of a superimposed, low-grade inflammatory reaction. The fact that they were approximately 50 per cent larger than the average normal glands suggests that true hyperplasia may well have been present earlier. The possibility has occurred to us that the irritative effect of infection may have been responsible in part for the peculiar hyperactivity of the cortical principle, which plays a role in the control of the electrolyte and water balances of the body.

The only postmortem evidence of other endocrine gland involvement was that referred to earlier regarding the hyaline changes in the cytoplasm of the basophilic cells of the pituitary, as described by Crooke (12). That this abnormality was not the factor reponsible for the disorder in electrolyte structure in our case is suggested by the fact that it was present also in the pituitary of the case of adrenal neoplasm just referred to, in which the blood electrolytes were normal. As evidence on the subject accumulates, it becomes more apparent that the one constant postmortem finding in cases showing the typical clinical syndrome described by Cushing as 'pituitary basophilism' and by others as the 'adrenal cortical syndrome' is this peculiar hyaline change in the cytoplasm of the pituitary basophil cells. Crooke described it as the one common postmortem finding in 12 cases showing the syndrome, 6 with basophil adenomata, 3 with neoplasms of the thymus gland and 3 with suprarenal cortical neoplasm or hyperplasia only. Seven of these cases showed the latter condition. Up to date Rasmussen (15) has found the same hyaline changes in 8 cases, with various other pathological changes present, such as chromophobic and basophilic adenoma of the pituitary and hyperplasia as well as neoplasm of the adrenal cortex. Graef and associates (16) have reported it in an additional case with carcinoma of the adrenal cortex. These authors quote a personal communication from Crooke indicating that he had found the hyaline cytoplasmic change in a total of 29 cases which had been examined by him up to Feb. 7, 1936. Whether or not this change in the pituitary basophils indicates secretory activity, as Crooke believes, or cytoplasmic degeneration is still problematical. Whether this change is primary and the associated findings, such as neoplasm of the thymus, pituitary or adrenal or hyperplasia of the latter, are secondary to it, or whether the reverse is the case, has not as yet been determined. As regards the present study, it would appear most likely from our present-day knowledge of suprarenal function that the peculiar electrolyte disturbance recorded is due to hyperfunction of the adrenals, rather than to any functional derangement of the pituitary.

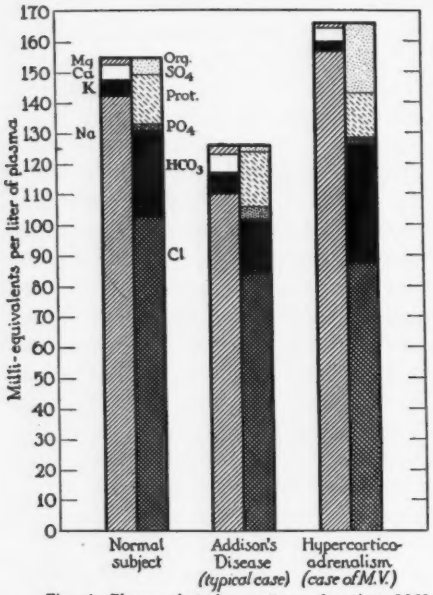

Fig. 4. Plasma electrolyte pattern of patient M.V. compared with that from a normal subject and that from a typical case of Addison's disease.

SUMMARY

A study of the plasma electrolytes was made in the case of a patient presenting a persistent tendency toward alkalosis in addition to the clinical features characteristic of the suprarenal cortical syndrome or Cushing's syndrome of pituitary basophilism.

Disturbances in the electrolyte pattern of the plasma were in most respects diametrically opposite to those found in a typical case of Addison's disease. The most striking abnormalities were the high concentrations of bicarbonate and sodium and the decrease in potassium and chloride. The plasma magnesium, calcium, inorganic phosphate and protein were reduced to levels slightly below normal. Before insulin therapy was instituted, the organic-acid-plus-sulphate fraction, estimated by difference between total base and determined acid constituents, was greatly increased in spite of the absence of ketonuria. This was completely reduced by insulin therapy. Neither cortin subcutaneously nor massive doses of sodium chloride by mouth caused a rise in the plasma chloride. A combination of the two was equally ineffective.

Potassium chloride ingestion, on the other hand, caused both the chloride and the potassium to return to normal levels, though the dosage was but one-fourth that of the sodium salt given previously. Coincidentally the plasma bicarbonate was temporarily reduced to near the normal value.

It is perhaps the very exceptional case of interrenalism only that suffers from such a marked disturbance of the acid-base metabolism as that described here.

Because of the striking and almost complete contrast between Addison's disease, which is so clearly due to hypofunction of the adrenal cortex, and the type of case presented here, we believe that the latter represents a true example of hyperfunction of the cortex, and so, might well be referred to by the designation 'hypercorticoadrenalism' or 'the hypercorticoadrenal syndrome'. It appears likely that, not a single hormone but several, are involved in the production of this complex disorder.

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CREATINURIA AND CREATINE TOLERANCE IN CHILDHOOD

WITH SPECIAL REFERENCE TO BONE AGE AND HYPOTHYROIDISM

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A severe degree of osseous retardation has been a consistent finding in preadolescent hypothyroidism (namely cretinism and childhood myxedema) when the condition has remained uncorrected for any length of time. This observation has also permitted the definition of a third form of childhood hypothyroidism, characterized primarily by dwarfism and psychomotor retardation, which does not fall within the accepted textbook description of cretinism or of childhood myxedema. (1, 2). The startling response of this type of patient to thyroid substitution has repeatedly justified our confidence in the validity of such a syndrome.

Due to the fact that a severe degree of bone retardation appeared to be the only common denominator in all of the three forms of hypothyroidism, extensive studies have been carried out for a number of years regarding the bone-age-thyroid relationship in general. Moderate degrees of osseous retardation are more common thany many suspect (an incidence of 17 per cent has been encountered in 560 unselected children). Basal metabolic rate determinations in young children are notoriously variable aand inconclusive. In our hands serum-cholesterol values were also uninformative in the borderline group. Some of these children, even in the absence of classic hypothyroid stigmata, responded to thyroid administration; some did not. It, therefore, appeared necessary to seek other biochemical aids in an effort to elucidate the problem.

The relationship of creatine metabolism to thyroid function is an intimate one. Increased creatinuria and diminished tolerance to ingested creatine has been demonstrated in hyperthyroidism (3, 4, 5). Conversely, in myxedema and cretinism, diminished creatinuria and increased tolerance to creatine has been revealed (6, 7). The purpose of this study was to observe creatine excretion in relationship to bone age in an effort to 1) confirm the hypothyroid etiology of the dwarfish child with psychomotor retardation and severely retarded bone age, who does not conform to the classic textbook description; 2) to observe the creatinuria in the moderately retarded bone-age group with the hope of contributing to the understanding of this condition.

MATERIAL

The observations in this report have been based on studies made in the past 2 years on 48 children ranging in age from 6 to 13 years. The children all

[1] This work was aided by a Grant from the St. Francis Foundation for Clinical Research, Santa Barbara, California.

came to the attention of the physician because of one or more of the following complaints: underweight; understature; poor resistance to respiratory infection; contact with tuberculosis. Forty-three of the children were preventorium patients;[2] the remainder were seen in the office. The presence of acute or chronic illness was ruled out. A complete history, physical examination and such essential laboratory data as tuberculin tests, Wassermann reactions, blood counts, and urine examinations were obtained in all instances. The bone age was determined roentgenographically, using the elbow and the carpal development as criteria. The roentgenograms were interpreted independently by a number of experienced observers, who were in remarkable accord (within

TABLE 1. VARIATIONS IN BASAL CREATINURIA AND CREATINE TOLERANCE. (10 cases)

	Initial					After Three Months			
	Age yr.	Weight lb.	Height in.	Basal Creatine mg.	Creatine Tolerance mg.	Weight lb.	Height in.	Basal Creatine mg.	Creatine Tolerance mg.
B.C.	10	62	55.3	208	1750	75	55.9	150	1729
M.M.	8	45	46.8	133	1206	47	46.8	200	1128
J.R.	8	47	48.3	168	2240	55	47.5	256	1646
V.L.	9	63	52.0	68	1708	67	52.0	39	1150
C.J.	12	68	58.5	195	1648	87	60.3	165	1649
G.E.	13	70	58.7	215	1275	83	60.3	238	1852
F.G.	11	59	52.5	109	2486	67	53.0	230	1863
J.R.	11	65	52.8	422	1300	70	53.5	227	1660
E.G.	12	82	61.8	160	1417	91	62.3	114	1768
H.F.	13	79	60.0	305	1135	92	61.3	418	2558
Av.	10.7	64	54.7	199	1617	73	55.3	204	1700
Percentage creatine retention per pound					0.82				0.69

1 year). The normal bone age is here defined as that presenting a deviation of bone development of less than 2 years from the average normal, according to the standards at our command (8). A moderate degree of bone retardation is here defined as a delay of 2 to 3 years. A severe degree of bone retardation, found in all instances of untreated hypothyroidism, consisted of a delay of more than 3 years.

METHOD

All patients were required to be at bed rest, under dietary restrictions for 3 successive days. Meat and meat products were eliminated, although milk, cheese and eggs were permitted. The fluid intake ranged between 1 and 2 quarts daily. Urine collections were made on the last 2 successive days of the 3-day period. The first 24-hour period of collection represented the spontaneous creatine excretion which is here defined as 'basal creatinuria'. The second represented the creatine excretion over a 24-hour period following the ingestion of 3.0 gms. of anhydrous creatine powder[3] mixed at the time in a glass of water and taken at 7 A.M. on an empty stomach. This latter may be defined

[2] The authors wish to acknowledge the kindly coöperation of Dr. Howard Eder, Medical Director of Sunshine Cottage, Santa Barbara, California.

[3] Creatine C.P. (anhydrous) obtained from Pfanstiehl Chemical Company, Waukegan, Illinois.

as the 'creatine tolerance'. Full precautions of preservation and prompt determination were exercised. The collection of urine was under nursing supervision. The constancy of preformed creatinine on the 2 successive days served as added assurance of the validity of 24-hour urine volumes. All urine was routinely examined for pathological evidence affecting the Jaffe color reaction. Creatine was determined 'in singles' by the method of Folin (9) on 1 or 2 cc. of urine. A known solution of creatine (1 gm. per l.) was determined concomitantly as a control on accuracy of method. The reliability of the technique employed was indicated by 98 to 102 per cent recovery. Standard precautions of colorimetry were observed. Creatine values herein expressed are in

TABLE 2. BASAL CREATINURIA AND CREATINE TOLERANCE IN CHILDREN OF BOTH SEXES OF NORMAL BONE AGE

Normal Girls (18 cases)						*Normal Boys* (13 Cases)					
	Age yr.	Weight lb.	Height in.	Basal Creatine mg.	Creatine Tolerance mg.		Age yr.	Weight lb.	Height in.	Basal Creatine mg.	Creatine Tolerance mg.
E.D.	6	43	46.8	321	1920	T.C.	5	55	49.5	45	1505
E.S.	7	53	48.0	80	1830	D.V.	6	45	48.3	45	1098
L.R.	7	51	49.0	125	2143	B.K.	8	51	51.4	115	1540
M.M.	8	45	46.8	133	1206	J.R.	8	48	47.3	125	1500
M.K.	8	46	49.5	267	1560	N.C.	8	54	49.0	277	2119
J.R.	8	47	48.3	168	2240	V.D.	8	51	50.0	147	1438
C.G.	8	55	50.5	108	2204	D.U.	9	66	53.3	99	1650
V.L.	9	63	52.0	68	1708	R.S.	9	52	51.7	165	1584
D.S.	9	55	49.8	198	2210	B.C.	10	62	55.0	208	1750
M.P.	10	62	54.8	115	1704	B.A.	11	94	60.5	60	1600
D.D.	10	56	52.3	189	1921	G.V.	11	81	58.0	140	910
G.F.	10	63	54.5	192	1443	E.C.	11	88	57.5	270	1575
N.P.	10	54	50.3	324	2176	B.C.	11	68	57.8	153	1148
E.L.	11	61	53.5	240	1028						
A.O.	11	93	60.0	270	1680						
B.P.	12	67	66.0	120	2312						
C.N.	12	68	58.5	195	1648						
G.E.	13	70	58.7	215	1275						
Average	9.4	58	52.7	185	1789	Average	8.8	63	53.0	142	1494

terms of milligrams equivalent of creatinine excreted in 24 hours. Values of creatine tolerance represent the total excretion during the 24-hour period following the ingestion of 3 gm. of creatine. Although appreciable amounts of creatine may still be excreted 48 and 72 hours after ingestion, only the first 24-hour period was utilized for the calculation of creatine tolerance. Subtraction of the preceding day's basal creatine value from the creatine tolerance figure revealed the amount actually excreted after ingestion of creatine. This value subtracted from 3.0 gm. (amount ingested) represents the amount of creatine actually retained. Reduction of the retained creatine to a percentage per pound of body weight, offers a suitable unit for purposes of comparison.

RESULTS

Before proceeding with the problem as outlined, namely, the relationship of creatine excretion to the status of bone development, it became necessary to evaluate the influence of such factors as weight and sex. While the number of observations was too few to permit finality of a statement, we wish to set down our impressions. An average gain in weight of 9 lb. in a group of 10 unselected children (table 1) over a 3-months period, caused little difference in the average basal creatinuria and the creatine tolerance of the group. Since this

TABLE 3. BASAL CREATINURIA AND CREATINE TOLERANCE CHILDREN OF RETARDED BONE AGE

Moderate Bone Retardation 12 cases (all males)						*Severe Bone Retardation* (both sexes, all hypothyroid)					
	Age yr.	Weight lb.	Height in.	Basal Creatine mg.	Creatine Tolerance mg.		Age yr.	Weight lb.	Height in.	Basal Creatine mg.	Creatine Tolerance mg.
B.F.	7	54	51.0	288	1489	J.S.	12	64	51.5	81	1345
R.R.	8	50	49.0	140	1146	E.T.	10	44	48.8	76	1440
G.T.	8	54	51.5	165	1168	A.O.	10	54	47.7	76	1079
F.S.	9	61	55.3	130	1938	H.J.	10	41	36.2	22	1298
R.B.	9	48	48.3	187	1365	C.H.	10	46	44.8	70	839
J.P.	9	58	54.0	218	1900						
F.G.	11	59	52.5	109	2486						
I.P.	11	64	53.8	252	2295						
J.R.	11	65	53.8	422	1300						
E.G.	12	82	61.8	160	1417						
L.C.	13	72	58.3	235	2000						
H.F.	13	79	60.0	305	1135						
Average	10.1	62.2	54.1	218	1637	Average	10.4	49.8	45.8	65	1200

gain in weight consisted primarily of fat (and fluid?) it implies a relative unimportance of these tissues in creatine excretion and tolerance. It does not however, invalidate the necessity of reducing creatine tolerance to the basis of a percentage of creatine retention per pound, since in the growing child increase in muscle mass undoubtedly roughly parallels increase in body weight. Perusal of values in table 1 although indicating little change in the average creatine excretion after a 3-months interval in the group as a whole, does show considerable fluctuation in basal creatinuria and creatine tolerance in individual cases. This fluctuation points to the advisability of repeated studies in individual instances.

Comparison of the creatine excretion between 18 girls and 13 boys, of normal bone age, discloses that girls excrete more basal creatine and have a higher tolerance figure (in actual fact a lower ingestion tolerance) than the boys. This is true both from the unaltered figures (table 2) and when the data is re-computed on the basis of a percentage creatine retention per pound (table 4). Because of the sex factor, boys only were selected to demonstrate the influence of a moderate degree of bone retardation on creatine excretion. Although excreting somewhat more basal creatine than those of normal bone age,

TABLE 4.—CREATINE RETENTION IN NORMAL, MODERATELY RETARDED, AND HYPOTHYROID (SEVERELY RETARDED) CHILDREN

Classified	No. of Cases	Age yr.	Weight lb.	Height in.	Av. Basal Creatine mg.	Av. Creatine Tolerance mg.	Av. percent. Creatine Retention	Percentage Retention per pound
Normal—								
Girls	18	9.4	58	52.7	185	1789	43.2	0.75
Boys	13	8.8	63	53.0	142	1494	54.6	0.87
Moderately retarded—								
Boys	12	10.1	62	54.1	218	1637	52.7	0.85
Hypothyroid— (severely retarded)								
Both sexes	5	10.4	49.8	45.8	65	1200	62.2	1.25

no appreciable difference in the tolerance could be observed (table 3) particularly when considered on the basis of a percentage retention per pound (table 4). In view of the scarcity of material, girls also had to be admitted within the group of 5 verified hypothyroid children. Table 3 shows that in each individual instance, as well as in the group as a whole, basal creatinuria was markedly depressed, and the creatine tolerance figures were quite low (in actual fact, a higher ingestion tolerance). The average in this group is considerably out of the range of the average for the other groups of children here considered, and becomes even more pronounced when creatine tolerance is reduced to a percentage of creatine retention per pound (table 4).

DISCUSSION

Of the 5 hypothyroid children presented, only 1 conformed to the classical description (*H.J.* a cretin). The remaining 4 children presented neither myxedema nor cretinism in the accepted sense of the word. They did, however, all present dwarfism, a severe degree of bone retardation, and psychomotor retardation. We do not know if the thyroid authorities would classify these children in one or the other of the textbook thyroid groups, namely, as cretins or as sufferers from myxedema, but if they would, there is something wrong with the basic textbook description which has remained unaltered for over forty years. We do know that because these patients do not fit into the classic description so carefully preserved from generation to generation, they were overlooked by numerous otherwise well qualified practitioners.

From our studies it would appear, therefore, that this inadequately described type is 4 times more common than classic cretinism or myxedema, and as such becomes of great practical importance so far as therapeusis is concerned. They have not only a severe degree of bone retardation, but their creatine excretion and creatine tolerance conforms to the well-recognized and classical types.

In this study very little has been found to throw light on the etiologic factors in children with moderately retarded bone age. The creatine values tend to be higher than the normal, revealing a trend in the opposite direction. Great caution should be exercised, however, in attaching too much diagnostic importance to the creatine excretion in such a patient. The creatine values notwithstanding, some of these moderately retarded children improve on thyroid and some do not. Clinical acumen and therapeutic trial remain of utmost importance in their management.

SUMMARY

Atypical as well as classical hypothyroid children present a severe degree of osseous retardation, diminished basal creatinuria and an increased tolerance to ingested creatine as compared with the normal.

Children presenting a moderate degree of osseous retardation without clinical evidence of subthyroidism were found to have an increased basal creatinuria and no deviation in tolerance to ingested creatine as compared with the normal.

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THE EFFECT OF THYROGLOBULIN AND RELATED SUBSTANCES ON THE O_2 CONSUMPTION OF LIVER IN VITRO[1]

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Following the isolation of thyroxin by Kendall, the determination of its chemical composition and its synthesis by Harington, and the demonstration that its administration could duplicate the physiological effects of the thyroid gland in vivo, the natural tendency was to regard it as the thyroid hormone. However, while the weight of evidence indicates that the active physiological principle of the thyroid is an iodin-containing substance, the nature of that substance is still obscure, provided it actually is only a single substance, which is itself uncertain. Assuming that it can be regarded as an entity, there is no doubt that thyroxin bears an important relationship to it. Tyrosin would naturally appear to be the ultimate precursor of thyroxin. Other substances, such as diiodothyronin, thyronin, and diiodotyrosin have demanded attention in view of their chemical similarity. Of the latter three, only diiodotyrosin has been shown to be present in the body. The effect of these substances has been studied, but even when they have been shown to have an effect on metabolism, the evidence has not indicated whether their physiological action may not have been an indirect one, that is, by virtue of their place in the elaboration by the thyroid of its hormone. This is equally true of the protein of the colloid material, thyroglobulin. In an attempt to throw further light on this matter, we have studied the effect of these substances on the oxygen consumption of tissues in vitro.

METHODS

In the present experiments the tissues used were guinea pig and rat liver, the O_2 consumption being determined in a Barcroft-Warburg differential manometer system. The guinea pigs and rats used varied as to sex and weight, but we have not noted these variations in the tables, since analysis showed no demonstrable relation to the effects produced. The animals were killed by a blow on the head, and the livers removed and sliced free-hand as rapidly as possible, except in one series of experiments when they were minced finely by chopping. The liver slices were in no case greater than $\frac{1}{3}$ mm. in thickness. The total amount of tissue in each respiration flask was usually 30 to 40 mg. dry weight. As a rule 3 flasks were used for control and 3 for test tissues. It should be observed that control and test tissues, in each experiment, were

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taken from the same animal. While there was considerable variation in the control QO_2 of different animals, the variations in the individual tissues were small, the average deviation of the QO_2 in individual animals, as will be seen in the tables, being about 0.2.

The medium was 3 cc. of a M/150 Sörensen phosphate buffer mixture in physiological saline, with glucose added to a concentration of 0.1 per cent. Experiments that we have performed in horse serum indicate that in the serum the O_2 consumption is consistently higher than in the medium we used. The pH of the medium, both in the control and the test flasks was adjusted usually to about 7.2 to 7.4, and was tested both before and after the experiment. In some of the earlier experiments this was done colorimetrically, later, with a Beckmann glass electrode pH meter. We have not included the data on pH in the tables except in a few cases in which they were of interest. No experiments are included in which there was any significant difference between the pH of the control and of the test media. The tendency was nearly always for a fall in the pH of the media during the experiment, amounting usually to 0.1 to 0.2 pH, and being greater in the case of rat liver than in that of guinea pig liver. Except in some experiments on diiodotyrosin, in which the pH fell as low as 6.85, in no case was it lower than 7.0 at the end of the experiment. In the experiments noted in table 1, in which the initial pH was purposely raised, the final pH varied from 7.4 to 7.8, the fall being somewhat greater, presumably, because of the lessened buffering capacity of the phosphate medium at these higher levels.

The experiments were usually begun at about 1 hour after the animals were killed, and the duration was ordinarily 1 hour, though frequently, in the earlier experiments, and sometimes, in the later ones, an extra hour was run to note the effect of deterioration. However, since this extra period yielded nothing of interest, our tables include only the first hour. During this period observations were made every 15 minutes. As a rule the QO_2 fell gradually as the experiment progressed, but not always. There was no striking difference between control and test tissues in this respect. In other words, a positive effect, when obtained, was present from the beginning of the observations.

RESULTS

Thyroxin

A good many conflicting experiments are reported in the literature on the in vitro effect of thyroxin. Ebine (1) found that thyroxin, added to rat liver and kidney tissue, increased the O_2 consumption of the tissues. (The anaerobic glycolysis was also increased. The anaerobic metabolism was studied in many of the researches, but we shall not be concerned with this phase of the problem). Davis, DaCosta, and Hastings (2) observed that the metabolism of intact frog heart was raised by thyroxin, and Davis and Hastings (3) made a similar observation on segments of limulus heart, but only after about 15 hours' incubation. Khayal and Scott (4) noted a rise in the rate of O_2 consumption in mouse uterus. Verebely (5) found thyroxin to stimulate the metabolism of brain tissue, but not liver or muscle. Paal (6) observed a positive effect on guinea pig thyroid, but thyroxin had no effect on liver. Other experimenters

TABLE 1. EFFECT OF THYROXIN

Date	Amt. of Thyroxin added[1]	Q_{O_2} Control	Q_{O_2} Test	Change per cent	Remarks
Guinea Pig Liver					
6/23/36	0.2 mg. added	4.1±0.2	4.1±0.2	0	
6/23	0.5 mg. added	2.5±0.1	3.5±0.2	+40	
6/25	0.5 mg. added	3.5±0.3	3.4±0.1	− 3	
6/25	0.5 mg. added	5.3±0.2	5.4±0.2	+ 2	
7/ 3	0.5 mg. added	3.2±0.1	3.8±0.3	+22	
7/16	0.5 mg. added	4.4±0.4	4.6±0.4	+ 7	
9/30	0.5 mg. added	2.8±0.1	2.9±0.2	+ 4	
10/ 1	0.5 mg. added	2.9±0.1	3.4±0.1	+17	
10/ 2	105γ	4.0±0.1	4.3±0.4	+ 8	
10/ 5	0.5 mg. added	4.1±0.4	3.8±0.3	− 5	
10/ 6	66γ	3.5±0.1	3.8±0.3	+ 9	
10/ 7	30γ	3.8±0.3	3.9±0.4	+ 3	
10/ 8	65γ	4.5±0.3	4.2±0.1	− 9	pH: Control 7.75; Test 7.70
10/ 9	162γ	4.0±0.2	4.0±0.4	0	pH: Control 8.0; Test 8.0
10/10	180γ	3.6±0.2	3.4±0.2	− 6	pH: Control 8.05; Test 8.05
10/13	171γ	5.3±0.2	5.0±0.3	− 6	pH: Control 7.95; Test 7.95
	AVERAGE	3.8	3.9	+ 5	
Rat Liver					
8/ 9/35	0.1 mg. added	8.2±0.1	8.2±0.4	0	
11/12/36	51γ	8.0±0.2	7.9±0.4	− 1	
11/13	58γ	9.2±0.4	8.6±0.2	− 7	
1/13/37	55γ	8.6±0.4	8.3±0.5	− 3	Tissue incubated in horse serum (see text)
1/18	28γ	9.1±0.1	9.1±0.1	0	Tissue incubated in horse serum (see text)
1/19	28γ	9.7±0.5	9.9	+ 2	Tissue incubated in horse serum (see text)
	AVERAGE	8.8	8.7	− 2	
Rat Liver. Low Thyroxin Concentrations					
8/27/36	conc. $=10^{-16}$	8.6±0.4	9.1±0.4	+ 6	
11/19	10^{-15}	7.2±0.4	8.7±0.3	+21	
11/23	10^{-15}	7.0±0.2	7.8±0.4	+11	
11/25	10^{-15}	8.7±0.3	8.5±0.2	− 2	
11/27	10^{-15}	6.4±0.4	6.4±0.4	0	Liver slices
11/30	10^{-15}	7.4±0.4	7.4±0.4	0	
12/ 1	10^{-15}	7.6±0.2	7.4±0.2	− 3	
12/18	10^{-7}	5.6±0.2	5.8±0.2	+ 4	
	AVERAGE	7.3	7.6	+ 5	
12/ 2/36	conc. $=10^{-15}$	2.4±0.1	2.8±0.1	+17	
12/ 8	10^{-15}	3.5±0.1	3.8±0.1	+ 9	
12/ 9	10^{-15}	3.2±0.1	3.1±0	− 3	
12/10	10^{-15}	3.4±0.1	3.3±0.3	− 3	
12/11	10^{-15}	2.7±0.1	3.0±0	+11	Minced Liver
12/17	10^{-7}	3.4±0.1	3.7±0.2	+ 9	
	AVERAGE	3.1	3.3	+ 6	

[1] Where the word 'added' is introduced after the amount, the actual amount of thyroxin in solution was not determined.

also found thyroxin to increase in vitro oxidations, but they used small concentrations, and we will deal with these later.

Many investigators were unable to observe any unequivocal evidence of a thyroxin effect. Anselmino, Eichler and Schlossmann (7); Fleischmann (8); Myhrmann (9); Paasch and Reinwein (10); Sturm (11); Verne (12) all found thyroxin to be without effect. In these experiments, a wide variety of tissues from different animals were studied. Hopping (13, 14) reported results that were on the whole negative. Some of the tissues studied by Paal, Verebely, and Hastings and his collaborators, also did not respond to thyroxin. No clear picture emerges from an analysis of the above researches to account for the discrepancies observed.

Our own investigations in the matter are as follows. Thyroxin solution (Hoffmann-La Roche, having a pH of about 11) was added to the phosphate-buffer solution to a concentration of usually 0.5 mg. per 3 cc. which was the amount of medium always used, and the pH brought, except where noted, to about 7.3. There was always precipitation. In the earlier experiments the amount of thyroxin in solution was not determined, but later, I_2 determinations were made, and from these, it can be said that at pH 7.3, between 50γ and 100γ of thyroxin were probably in solution. In the later experiments, as noted in table 1, the amount in solution was computed from the I_2 determinations.[2]

Guinea Pig Liver. The results are to be seen in table 1. The average QO_2 of the control tissues, in 16 experiments, was 3.8; the QO_2 of the tissues to which thyroxin had been added was 3.9, a negligible difference. In one experiment, that of Jan. 23, there was an unmistakable rise of 40 per cent; in two others, July 3 and Oct. 1, a somewhat more equivocal one. In these 3 experiments the control QO_2 was low. Whether this was of any significance we are unable to say, although other experiments (for example, Sept. 30) having a low control QO_2, showed no thyroxin effect. To increase the amount of thyroxin in solution, we raised the pH of the medium in some experiments, as noted in the table. This did not result in an increased O_2 consumption of the test tissues. The results seem to indicate that so far as guinea pig liver is concerned, thyroxin in vitro does not increase the O_2 consumption in the amounts used.

Rat Liver. A similar conclusion is to be reached from the experiments on rat liver. In 7 experiments, the average control QO_2 was 8.8; that of the test tissues was 8.7, and in no single case was a positive effect seen. In 3 of the experiments, the tissues (both control and test) were previously incubated for 4 hours in horse serum. This did not affect the negative results of adding thyroxin to the test tissues in the respiration flasks.

A point as to concentrations of thyroxin has been several times raised in the literature. Ahlgren (15), using the methylene blue technique, found an increased rate of oxidation when thyroxin was added to frog muscle pulp in a concentration of 10^{-14}, and stated that concentrations greater than 10^{-9} actually inhibited oxidations. His results with rabbit muscle, on the other hand, were negative. Mansfeld (16) obtained a positive effect with concentrations of about 10^{-12}, which disappeared when the concentration was raised to 10^{-8}

[2] The I_2 determinations were made for us by Ruth Guild, to whom we wish to express our indebtedness.

TABLE 2. EFFECT OF THYROGLOBULIN

Date	Amt. of Thyroglobulin added mg.	Q_{O_2} Control	Q_{O_2} Test	Q_{O_2} Change per cent	Remarks
		Guinea Pig Liver			
10/14/36	7.3	4.2±0	5.9±0.4	+40	
10/15	7.3	3.9±0.1	6.0±0.2	+54	
10/16	7.3	3.3±0.1	4.7±0.2	+42	
10/19	7.3	3.5±0.2	5.6±0.1	+60	
10/20	7.3	3.6±0.1	6.5±0.2	+81	
1/28/37	6.1	2.8±0	4.5	+61	
1/28	10.0	2.8±0	4.4	+57	
2/ 2	10.0	3.5±0.1	4.7±0.1	+34	
2/ 3	10.0	2.6±0.2	3.5±0.1	+35	
2/ 4	10.0	2.5±0	3.3±0.2	+32	
2/11	10.0	3.1±0.3	3.6±0.1	+16	
2/15	1.0 (?)	3.2±0.2	5.1±0.1	+59	
2/16	7.3	4.4±0.1	5.9±0	+34	
2/18	7.3	4.1±0.2	5.5±0.1	+34	
2/19	10.0	4.2±0.1	6.0±0.1	+43	
	AVERAGE	3.4	5.0	+45	
		Rat Liver			
10/29/36	3.9	7.9±0.2	9.2±0.1[1]	+16	
11/ 5	3.9	7.0±0.3	10.0±0.3	+43	
11/ 9	3.9	8.4±0.2	11.2±0.5	+33	
11/10	3.9	7.1±0.2	9.8±0.2	+38	
11/20	1.7 (?)	4.5±0.1	11.2±0.3	+149	
11/24	1.7 (?)	6.3	9.7±0.2	+54	
12/22	7.0	7.1±0.1	9.3±0.7	+31	
1/25/37	6.1	8.2±0.4	9.5±0.1	+16	Tissue incubated in horse serum (see text)
1/26	6.1	7.6±0.4	10.1±0.9[1]	+33	Tissue incubated in horse serum (see text)
1/27	6.1	7.2±0.1	8.0±0.3	+11	
1/29	19.2	5.4±0.2	5.9±0.2	+11	
2/ 1	10.0	7.4±0.1	7.2±0.2	− 3	
2/ 8	10.0	7.6±0.3	8.4±0.3	+11	
2/ 9	10.0	8.1±0	8.6±0.3	+ 6	
2/10	10.0	7.3±0.3	8.0±0.1	+10	
3/19	10.0	5.1±0	8.3±0.1	+63	Same Tissue
3/19	5.0	5.1±0	6.3±0.2	+24	
3/22	7.8	5.6±0.3	8.7±0.2	+55	Same Tissue
3/22	3.9	5.6±0.3	7.4±0.1	+32	
3/24	7.8	5.2±0.2	7.3±0.3	+40	
5/ 6	8.3	8.0±0.4	7.9±0.1	− 1	
5/ 7	8.3	7.1±0.1	8.8±0.1	+24	
	AVERAGE	6.8	9.2	+33	

[1] The variation was from Q_{O_2} 9.2 to 10.9. We suspect that the lower of these two figures is an error, as the slices were cut long, and showed a tendency to clump.

Haarman (17) came to a similar conclusion, using skeletal muscle and liver of guinea pig, rabbit and cat, and obtaining the largest increases in O_2 consumption with concentrations of 10^{-14} and 10^{-16}. At concentrations of 10^{-5} an inhibition amounting to as much as 30 to 40 per cent was observed. The experiments of Reinwein and Singer (18) on guinea pig liver, using concentrations of 10^{-8} and 10^{-12} showed doubtful increases, and later experiments of Paasch and Reinwein (10) on rat diaphragm were negative. In the latter experiments,

however, the lowest concentration used was 10^{-8}, which was also true in the negative results of Anselmino, Eichler, and Schlossmann (7), and of Rothschild (19).

In view of the above evidence, we have performed certain experiments at similar low concentrations, the results of which are seen in table 1. Most of the experiments were made with thyroxin concentrations of 10^{-15}, with one of 10^{-16} and two of 10^{-7}. Both sliced and minced rat liver were used, and in 14 experiments the results were almost consistently negative. We feel justified in saying that, so far as this tissue is concerned, thyroxin has no effect either at

TABLE 3. EFFECT OF DIIODOTHYRONIN. GUINEA PIG LIVER

Date	Amt. of Diiodothyronin added	Q_{O_2}		
		Control	Test	Change per cent
3/ 8/37	111γ	3.9±0.2	3.0±0.1	−23
3/ 9	111γ	5.2±0.3	3.4±0.3	−33
3/10	111γ	4.2±0.4	3.0±0.1	−29
3/16	10γ	3.1±0.2	3.3±0.1	+ 6
3/18	14γ	3.2±0.1	3.2±0	0
3/25	50γ	2.8±0.1	3.8±0.1	+36
3/26[1]	96γ	2.8±0.1	3.6±0.4	+29
3/26[1]	50γ	2.8±0.1	4.2±0.1	+50
3/29	100γ	4.8±0.5	5.0±0	+ 4
3/29	96γ	4.8±0.5	4.6±0.2	− 4
3/30	96γ	5.1±0.2	4.9±0	− 4
3/31	96γ	4.5±0.3	4.0±0.1	−11
4/ 1	96γ	4.7±0.3	4.3±0.1	− 9
4/ 2	96γ	4.6±0.2	4.8±0.2	+ 4
4/ 2	100γ	4.6±0	4.9±0	+ 6
4/ 5	100γ	4.5±0.4	4.9±0.1	+ 9
4/ 7	100γ	5.0±0.2	5.0±0.1	0
4/ 8	74γ	3.1±0.2	3.4±0.1	+10
4/ 9	100γ	4.2±0.2	4.8±0.1	+14
4/12	100γ	3.4±0.2	4.6±0.1	+35
4/13	100γ	3.5	3.9±0.2	+11
4/14	100γ	3.9	4.2±0.2	+ 8
4/15	100γ	2.5	4.2±0.1	+68
4/23	100γ	3.5±0.3	4.0±0.1	+14
	AVERAGE	3.9	4.1	+ 8

[1] Same tissue.

the greater or the lower concentrations. The actual concentration of thyroxin in the tissue is of course impossible to state. From blood I^2 determinations, it can be guessed that the blood thyroxin might be in a concentration as high as 10^{-8}, but even this implies certain assumptions, especially the one that thyroxin, as such, exists in the blood at all. Our general conclusion is that thyroxin is without effect on the O_2 consumption of guinea pig and rat liver tissue in vitro.

Thyroglobulin

The thyroglobulin was prepared from fresh hog thyroids. The latter was ground and extracted twice with 0.9 per cent NaCl. The extracts were precipitated 3 times with half saturated $(NH_4)_2SO_4$. The last precipitate was taken up in NaCl, dialyzed to get rid of salts, concentrated by pervaporation in cello-

phane bags, defatted with ether, and finally dried under reduced pressure. The final product was soluble in water as well as in the experimental buffer medium. Two separate batches of this material were used in the present observations, one containing 0.7 per cent I_2; the other 0.6 per cent I_2. The product as obtained was not sterile, and bacterial contamination complicated some of the earliest observations. Thereafter, solutions were made as needed, and sterilized by filtering in a Seitz filter. The results obtained are to be seen in table 2.

Guinea Pig Liver. In 15 experiments, the average QO_2 of the control tissues was 3.4; in the test tissues it was 5.0, an average increase of 45 per cent. The increase varied from 16 per cent to as high as 81 per cent, but was invariably present. The reason for the fact that the effect differed markedly in different animals is obscure. We have analyzed the factors of age, sex,

TABLE 4. EFFECT OF THYRONIN. GUINEA PIG LIVER

Date	Amt. of Thyronin added	QO_2		
		Control	Test	Change per cent
3/ 8/37	300γ	3.9±0.2	2.7±0.1	−31
3/ 9	300γ	5.2±0.3	3.5±0.2	−33
3/10	300γ	4.2±0.4	2.9±0.1	−31
3/16	30γ	3.1±0.2	3.0±0.1	− 3
3/18	60γ	3.2±0.1	3.3±0.1	+ 3
3/23	150γ	3.2±0.2	3.3±0.6	+ 3
3/25	150γ	2.8±0.1	2.8±0.2	0
3/31	300γ	4.5±0.4	4.7±0.1	+ 4
4/ 5	300γ	5.0±0.2	5.2±0.1	+ 4
4/ 7	300γ	3.1±0.2	3.0±0.1	− 3
4/ 8	300γ	4.2±0.2	3.8±0.2	−10
4/ 9	300γ	3.4±0.2	3.6±0.1	+ 6
4/12	300γ	3.5	3.4±0.1	− 3
4/13	300γ	4.5±0.1	4.7±0.3	+ 4
4/20	300γ	4.7±0.1	4.7±0.3	0
4/21	300γ	4.5±0.3	4.2±0.1	− 7
	AVERAGE	3.9	3.7	− 6

initially low QO_2, of the control tissues, and pH; without finding any definite correlation. In any case there is consistently a positive effect upon the O_2 consumption. That this is not a simple protein specific dynamic action is indicated by the fact that a comparable amount of casein was without effect. We were at pains to give comparable amounts of iodine in the thyroglobulin and thyroxin experiments. Thus, 10 mg. of thyroglobulin would contain about 60γ of I_2; this amount of I_2 would be present in about 90γ of thyroxin. Both more and less than this quantity of thyroxin produced no effect on the O_2 consumption.

Rat Liver. Here the stimulating effect of thyroglobulin was not so consistently seen as in the case of guinea pig liver, nevertheless, in 20 of 22 experiments the addition of thyroglobulin to the tissue resulted in a rise in the O_2 consumption, and the increase was usually unmistakable. Again there was considerable variation in different animals. On two days (March 19 and 22) we used different amounts of thyroglobulin in the presence of tissue from the same animal, and in a rough way, but probably not exactly enough for pur-

poses of assay, the effect was a function of the amount of thyroglobulin used. On March 24, 7.8 mg. of the material produced an increase of 40 per cent; on the same tissue 0.78 mg. (not noted in tables) raised the O_2 consumption 13 per cent.

In contrast with thyroxin, it seems clear that thyroglobulin acted as a powerful stimulant to the oxidations in liver tissue.

Diiodothyronin

We performed 24 experiments with diiodothyronin (Schering-Kahlbaum). The results are difficult of interpretation. If one averages the figures, there is practically no difference between the QO_2 of the control and the test tissues, which were 3.9 and 4.1 respectively (see table 3). But the variations from this are not to be accounted for by the error of the method, which was about $\pm$ 5 per cent. In 6 of the experiments there was an unmistakably stimulating effect on the O_2 consumption; in 3 there was an equally unmistakable decrease, and in the remaining 15 there was either no change or a small one in either direction. The only possible correlation that we have been able to find is with the height of the control QO_2. Generally speaking, the lower the control QO_2, the greater the tendency for an increase on adding diiodothyronin, and vice versa, but this is not unequivocal, as a glance at the table will show. It may be that diiodothyronin is capable of stimulating liver metabolism in vitro, provided the oxidations have for some reason been previously depressed, but not otherwise.

Thyronin

Of 16 experiments performed with this substance (obtained from Hoffmann-La Roche), all but 3 showed practically no difference between the control and the test tissues (see table 4). After observing a definite decrease in the first 3 experiments (as in the case of diiodothyronin, the corresponding experiments of which were incidentally performed on the same group of guinea pigs), we here attempted, as with diiodothyronin, to abolish the effect by decreasing the amount of thyronin. This abolition actually occurred, as will be seen in the table, but was apparently not a function of the amount of the material introduced, for we were never again able to observe an effect due to this substance. We are forced to the conclusion that thyronin is without the power to increase the O_2 consumption of liver tissue, though it may in a few cases depress it.

Diiodotyrosin

Guinea Pig Liver. Six experiments were performed, and while there was a slight tendency toward a depression of the O_2 consumption, the change was very slight. On the whole it might be said that diiodotyrosin was without influence.

Rat Liver. In this series 11 experiments were performed, and in every case the addition of diiodotyrosin depressed the O_2 consumption, irrespective of the height of the control QO_2, though in general, the higher this was, the greater the depression. The average decrease was 19 per cent (see table 5).

DISCUSSION

The failure of thyroxin to increase the oxidations of liver tissue in vitro, coupled with the fact that thyroglobulin has a definite stimulating effect, lends weight to the hypothesis that thyroxin is not the thyroid hormone. Moreover, it seems to indicate that liver tissue, at any rate, is incapable (within the time limits of the experiment) of catalyzing the formation of the hormone from thyroxin. In view of the effect of thyroxin on the intact animal one must suppose, failing more precise evidence, that the hormone can be synthesized, with thyroxin as an intermediary product, only in the thyroid gland itself.

TABLE 5. EFFECT OF DIIODOTYROSIN

Date	Amt. of Diiodotyrosin added mg.	Q_{O_2}		
		Control	Test	Change per cent
		Guinea Pig Liver		
7/16/36	2	3.8±0.2	3.1±0.5	−18
10/22	2	5.4±0.1	5.1±0.2	− 6
10/23	2	4.6±0.4	4.2±0.4	− 9
10/26	2	3.9±0.4	4.4±0.2	+13
10/27	10	3.5±0.1	3.5±0.4	0
11/17	2	3.8±0.5	3.7±0.2	− 3
	AVERAGE	4.2	4.0	− 4
		Rat Liver		
8/15/35	2	10.0±0.4	6.5±0	−35
8/29	2	11.3±0.5	7.8±0.2	−31
9/12	2	7.8±0.4	4.9±0.4	−37
11/23	2	8.9±0.2	6.9±0.4	−23
11/25	2	8.5±0.2	7.1±0.1	−17
10/28/36	2	7.3±0.2	6.9±0.1	− 6
10/30	2	7.3±0.2	6.0±0.1	−18
11/ 2	2	6.3±0.2	5.8±0.2	− 8
11/ 3	2	6.7±0.3	5.7±0.2	−15
11/ 4	2	7.9±0.2	6.9±0.2	−13
11/16	2	7.2±0.3	6.7±0.2	− 7
	AVERAGE	8.1	6.5	−19

On the other hand, while it is perhaps fair to assume as a working hypothesis that the thyroglobulin effect is due to the active thyroid principle, the experiments do not prove that thyroglobulin, in whole or in part, is actually the stimulating principle itself, for it is possible that the liver may be able to elaborate the latter from thyroglobulin but not from thyroxin. Still assuming that thyroxin is in the pathway of the synthesis of the thyroid hormone, one must conceive of thyroglobulin as either containing the active substance, or of being a stage nearer its final form than is thyroxin.

The experiments would appear to rule out the idea that thyroglobulin is simply a storage form for the hormone in the thyroid colloid, inactive in itself, but capable of being broken down by the thyroid into an active form. If secreted as such into the blood stream—and there is evidence from the work

of Hektoen, Carlson and Shulhof (20, 21) that it may be—it can clearly be utilized by the liver, at least, either directly or indirectly, and hence may be said to fulfill the posulates of the hormone, even though it may still have to undergo further changes in such an outlying organ.

The conflicting effects of diiodothyronin are puzzling. It is possible that the liver can synthesize a stimulating substance from it, but only under certain conditions, and that in the experiments in which a definite rise in O_2 consumption was obtained such a synthesis occurred. If so, it would indicate a pathway for the synthesis not including thyroxin. There is no reason, in view of the much more consistently positive effects of thyroglobulin, to suppose that diiodothyronin is itself the hormone, particularly as it has, in the intact animal, so much smaller an effect on metabolism than either thyroxin or thyroglobulin.

As to thyronin, Harington and Barger have shown the difficulty of synthesizing thyroxin from this substance, which tends to rule it out of one pathway for the elaboration of the hormone. Moreover, in recent unpublished experiments in this laboratory, thyronin, alone of all the substances so far discussed in this paper, has proved to be incapable of raising the metabolism of the intact animal. These facts together with the negative results of the experiments with this substance here reported, make us suspect that thyronin does not lie in the pathway of the elaboration of the hormone. The evidence lends no support to the hypothesis of Paal (22) that thyronin is the thyroid hormone.

Diiodotyrosin would appear, for one thing, to be in the pathway for the synthesis of thyroxin, and Salter and Pearson (23) have shown that the diiodotyrosin fraction of peptone produced by pepsin digestion of thyroglobulin can be resynthesized into an active thyroglobulin. Moreover, we have previously shown that diiodotyrosin, while its effect is not quantitatively comparable with that of thyroxin, definitely increases the metabolism of the intact animal. Nevertheless, in the present experiments it not only failed to stimulate the O_2 consumption of liver in vitro, but in the case of rat liver, consistently depressed it. We have no reasonable explanation to offer for this inhibitory action of diiodotyrosin. As for its failure to stimulate, it would seem that if diiodotyrosin is, as would appear inevitable, a necessary step in the formation of the thyroid hormone, the liver, at least, is incapable of carrying this synthesis further.

SUMMARY

The effect of certain substances upon the O_2 consumption of guinea pig and rat liver in vitro has been studied, with the following results. Thyroxin had no effect upon either tissue, while thyroglobulin (hog) markedly increased the O_2 consumption of both. Diiodothyronin was inconstant, occasionally either raising or depressing the O_2 consumption, but usually having a negligible effect. Except for a few instances of depression, thryronin had no effect. Diiodotyrosin did not appreciably change the O^2 consumption of guinea pig liver, but consistently depressed that of rat liver. It is postulated that thyroxin is not the thyroid hormone, and that the latter is either thyroglobulin or an integral part of it.

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EFFECT OF THYROIDECTOMY AND THYROID FEEDING IN GEESE ON THE BASAL METABOLISM AT DIFFERENT TEMPERATURES

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Thyroidectomy, in whatever animal species it has been performed, has invariably resulted in a profound lowering of the basal level of the heat production. The metabolic reactions of thyroidectomized animals to changes in environmental temperature have not been adequately investigated, however, although there are many indications that the thyroid is an important part of the body's internal mechanisms for the regulation of its temperature under widely varying environmental conditions (1-8).

The bird, as well as the mammal, has successfully met the problem of the maintenance of constant body temperature under environmental temperatures which may vary seasonally as much as 35°C. or more. The thyroid glands are possibly involved in this control, in birds as well as in mammals. Avian thyroidectomy has been practically unattacked due, probably, to the difficulty of the removal of the glands from their location within the chest. Riddle (9, and personal communication) has been able to remove the glands in pigeons and has reported data on one bird with complete ablation. In this pigeon the B.M.R. was lowered about 40 per cent after thyroidectomy. Preliminary observations on ducks and chickens convinced us that the operation was feasible in a large bird and that the goose would be particularly suitable.

For many years the Nutrition Laboratory has used geese in metabolic investigations, and the basal level of metabolism in this animal is well known (10). Furthermore, in these past experiments a paradoxical thermogenic reaction of this animal to low environmental temperatures had been suggested. It was noted that certain geese had not responded to low environmental temperatures by an increased heat production, such as is characteristic of most warm-blooded animals. The present paper reports a further study of heat regulation in the goose as affected by low temperatures, and by thyroidectomy and thyroid feeding.

METHODS AND PROCEDURE

Animals. Thirteen geese of mixed domestic breed (Toulouse and Embden) were used. Seven were males, 2 were females and in 4 the sex was not determined. Five of these were thyroidectomized. One thyroidectomized goose died soon after the operation as the result of hemorrhage; the other 4 lived from 6 months to 2 years after the operation. The animals were procured from a poultry dealer or from local farms and the exact ages were unknown; judg-

ing from size and appearance, they were from 1 to 3 or more years old. One weighed 7.1 kg.; the other 12 weighed between 3.9 and 5.9 kg. when purchased.

The geese were penned indoors at a fairly constant temperature of about 22°C., or on the roof, or on the lawn during the summer months. For adaptation to low temperatures they were placed in a cold room at 4° to 10°C. or at 16°C. at least 24 hours before making metabolic measurements at those temperatures.

The diet was a mixed one of grain, fresh leafy vegetables, and grass in the summer, with water ad libitum. Cod liver oil, in capsules, was administered twice weekly. When thyroid was administered, it was given as tablets of desiccated thyroid (Burroughs Wellcome Co.) in dosages of 0.4 to 4.4 grains (U.S.P.) per day.

Thyroidectomy. The thyroid glands in the mixed-breed domestic goose of 4 to 7 kg. body weight are round or slightly oval bodies, 7 to 12 mm. in diameter, encapsulated, dark red in color, located in the thorax, one on the ventral side of each carotid artery within 1 or 2 cm. of its origin from the aorta. Each gland is closely attached by a short stalk to a carotid artery. Through the short stalk pass the thyroid artery and vein. Other smaller vessels pass to and from the thyroid in the thin connective tissue veils which partially cover and bind together gland, carotid artery and veins. An approach through the side of the thorax was contemplated but the large pectoral muscles, the fusion of the ribs, and the necessity of opening both sides made this unsatisfactory. The approach finally used was through the large arch of the furcula and pectoral girdle.

The goose was anesthetized with ether and tied, back downward, on an animal board fastened at an angle of about 30°, with the head at the high end. Feathers and down were cut close to the skin over an area of the breast, sternum and the ventral part of the base of the neck. After sterilization of the skin an incision about 3 inches long was made, extending from the anterior end of the sternum to the neck. The soft tissues and sheets of fascia covering the arch of the furcula were then dissected. When the thoracic cavity was thus opened the respiration of the animal changed in character, becoming shallower and more rapid. Ventilation was barely adequate. It was sometimes difficult to give enough ether for surgical anesthesia, but it was not necessary to use artificial respiration.

Illumination of the cavity through the arch of the furcula was provided by a focusing head-lamp. The fascial veils surrounding each thyroid, carotid artery and jugular vein were then separated and cleared away from the gland and stalk. Bleeding from the vessels running to and from the thyroid in this connective tissue was often troublesome and difficult to control. A specially devised snare was used to compress the blood vessels in the stalk and to aid in the placing of a silk ligature which was tied around the stalk. The thyroid was detached by burning through the stalk with a heated wire loop. The tying of the ligature tightly enough to prevent hemorrhage was the most difficult part of the operation. In one goose a ligature slipped and a fatal hemorrhage into the thorax occurred about 12 hours after the operation.

The parathyroids in the goose are discrete bodies, lighter in color than the

thyroid and lie posterior to the thyroid, although often very close to it. It was found possible to leave the parathyroids intact in every case.

After both thyroids were excised the fascial and skin openings were closed by sewing, care being taken to close the cavity at the end of a deep expiration. Recovery was prompt, with no infection resulting.

An autopsy was eventually made on all of the thyroidectomized geese, and search made for regenerated or accessory thyroid gland tissue. Sections were cut of suspected pieces of tissue near the site of the gland. No remaining thyroid tissue was found in any of the 5 geese operated upon. The parathyroids had been left intact in every case.

Respiration apparatus. The apparatus was of the open-circuit type. It consisted of a 27-liter chamber, ventilated by means of a blower at a rate of about 4 liters per minute. The outgoing air was metered and a continuous sample withdrawn (11). The air samples were analyzed by the use of the Carpenter gas analysis apparatus (12). A water jacket surrounded the metabolism chamber and the desired temperature of the chamber was maintained by regulating the temperature of the water bath or, on numerous occasions, by placing the whole apparatus in a cold room. Activity of the animal was recorded by means of the arrangement described by Benedict and Homans (13), but the whole metabolism chamber, instead of only the animal, was suspended on the pivoted platform.

Metabolism determinations. For basal values of heat production several specific conditions are necessary. *1).* The animal must show, as nearly as possible, complete absence of muscular activity. In general it may be stated that in the long experience of the Nutrition Laboratory with different mammals and birds, the goose fulfills this requirement as well as, or better than, any other animal. A very short period of training is the most that is necessary to secure satisfactory, quiet periods. As an additional precaution, the goose in the metabolism chamber was placed in a loosely fitting jacket of wire mesh, which prevented the animal from standing or extending its wings. *2).* The basal measurement must be made at an environmental temperature within the zone of thermic neutrality, so that thermogenesis will not be stimulated. With most mammals and with pigeons and doves (14) this environmental temperature is not far from 28°C. Certain species show wide deviations from this. The heavily wooled sheep, for example, shows no significant alteration in basal metabolism when the environmental temperature is as low as 10°C. (15). The goose has a thick covering of feathers and down, and large fat deposits. Many experiments at the Nutrition Laboratory, including the present ones, have indicated that this animal also has a wide zone of thermic neutrality, extending from approximately 17° to 28°C. We considered it advisable to make the basal measurements at a little below 28°C. and actually used temperatures of 21° to 24°C. for most of them. *3).* The temperature under which an animal is kept prior to the basal metabolism determination should be approximately the same as that at which it is measured. In all of these experiments, the geese were kept for 24 hours preceding a determination at the same environmental temperature at which they were to be measured,

TABLE 1. BASAL METABOLISM OF NORMAL GEESE AT THERMIC NEUTRALITY (21°C. TO 24°C.), FASTED FOR 24 TO 30 HOURS

Goose No. and date	Body Wt. Kg.	Previous Environmental Temp.°C.	Rectal Temp. at end of Exp. °C.	R.Q.	Heat Production per 24 hr.		
					Total Cal.	Per kg. Cal.	Per 10 $\times W^{2/3}$ Cal.
104							
2/16/34	5.48	21	—	.71	293	53.5	943
2/20/34	5.49	22	—	.72	298	54.3	959
3/ 9/34	5.38	23	41.4	.70	295	54.8	961
Average	5.45	22		.71	295	54.2	954
108							
4/ 3/34	4.21	21	41.3	.71	242	57.5	929
4/ 6/34	4.22	23	41.4	.73	260	61.6	995
Average	4.22	22	41.4	.72	251	59.6	962
109							
3/12/34	4.01	20	40.8	.72	235	58.6	933
3/20/34	4.05	23	40.7	.70	235	57.9	923
Average	4.03	22	40.8	.71	235	58.3	928
110							
5/19/34	3.71	22	40.9	.71	249	67.1	1039
5/26/34	3.78	21	41.0	.72	260	68.6	1068
6/20/34	4.34	22	41.1	.70	289	66.7	1089
Average	3.94	22	41.0	.71	266	67.5	1065
111							
8/10/34	5.88	28	40.7	.71	315	53.5	965
10/ 5/34	7.23	18	40.9	.71	406	56.2	1086
3/28/35	7.51	22	41.1	.76	408	54.4	1048
5/16/35	7.57	22	41.2	.71	418	55.2	1084
Average	7.05	22	41.0	.72	382	54.8	1046
112							
6/25/34	5.72	27	41.1	.69	299	52.3	935
6/29/34	5.61	25	41.3	.73	349	62.3	1107
7/ 6/34	5.76	30	41.5	.70	322	55.8	1001
10/ 4/34	6.26	18	41.1	.74	355	56.7	1045
10/ 8/34	6.10	18	40.9	.74	362	59.3	1083
10/23/34	5.65	24	40.8	.71	265	46.9	835
10/29/34	5.60	20	40.9	.70	291	52.0	924
10/30/34	5.52	27	40.7	.70	264	47.8	844
1/24/35	5.66	21	40.8	.73	391	69.1	1231
Average	5.76	23	41.0	.71	322	55.9	1001
113							
8/ 9/34	4.53	27	40.9	.71	249	54.8	907
10/ 3/34	4.93	18	40.9	.69	283	57.4	977
Average	4.78	21	41.0	.69	265	55.5	934
114							
8/ 9/34	4.48	27	40.8	.71	269	60.0	989
10/ 3/34	6.32	18	41.6	.69	304	48.1	889
10/ 9/34	6.14	18	41.0	.70	310	50.4	923
10/24/34	5.87	24	41.7	.71	281	47.9	863
Average	5.70	22	41.3	.70	291	51.4	916
115							
2/15/35	4.45	23	41.0	.70	301	67.7	1113
4/ 4/35	4.22	20	41.2	.70	287	67.9	1098
4/17/35	3.93	20	—	.70	258	65.5	1035
5/15/35	3.73	23	41.4	.71	207	55.6	862
5/22/35	3.80	23	41.2	.69	214	56.2	877
5/25/35	3.82	19	41.3	.72	226	59.2	925
Average	3.99	21	41.2	.70	249	62.0	985

TABLE 1.—*Continued*

Goose No. and date	Body Wt. Kg.	Previous Environmental Temp. °C.	Rectal Temp. at end of Exp. °C.	R.Q.	Heat Production per 24 hr.		
					Total Cal.	Per kg. Cal.	Per 10 $\times W^{2/3}$ Cal.
116							
2/ 4/35	6.41	22	41.4	.70	381	59.5	1106
4/ 5/35	5.47	22	41.4	.69	333	60.8	1072
5/23/35	5.59	19	41.0	.70	327	59.5	1037
6/ 3/35	6.12	21	42.2	.69	379	61.9	1132
Average	5.90	21	41.5	.70	355	60.4	1087
117							
2/15/35	4.78	23	41.7	.70	309	64.7	1090
4/ 5/35	3.93	22	40.9	.71	286	72.8	1150
Average	4.36	23	41.3	.71	298	68.8	1120
118							
4/29/35	4.51	22	41.4	.74	257	57.0	942
4/23/35	5.41	23	—	.70	316	58.5	1027
4/26/35	5.36	22	—	.71	288	53.8	941
5/ 2/35	5.32	22	41.5	.68	288	54.0	944
5/17/35	5.46	23	—	.71	290	53.2	936
6/ 5/35	6.33	22	—	.71	346	54.7	1011
6/13/35	6.59	24	40.7	.70	347	52.7	988
7/17/35	6.55	25	41.3	.69	280	42.7	800
2/ 9/36	6.86	22	—	.69	283	41.1	782
Average	5.82	23	41.2	.70	299	52.0	930
Total Average	5.08	22	41.2	.71	293	58.4	994

whether this was 0 to 10°, 16° or 24°C. *4)*. Digestive activity should be absent. This is assured in the goose, as in most birds, by a fast of 24 hours, which was used in all of the experiments.

RESULTS

Although only adult geese were used, a direct comparison of the total heat production in different individuals cannot always be made because of the range in weight from 3.7 to 7.6 kg., and because of large changes in weight in some animals, more than 2 kg. in two instances. The values are therefore expressed as total heat production, as heat per kg. of body weight and as heat referred to the two-thirds power of the body weight. Practically, for many of the basal values and for most of the comparisons made, it is immaterial whether increases and decreases in metabolism are calculated on the basis of the total heat production, the heat production per kg. of body weight, or the heat production referred to the two-thirds power of the body weight. The significant findings are the percentage changes, without special regard to the absolute values of the basal levels.

The results of the basal measurements for 12 normal geese at environmental temperatures of 21° to 24°C., or within the zone of thermic neutrality, are given in table 1. The average for each animal represents the results of experiments on 2 to 9 separate days. Usually 4 or more consecutive determinations were made on each day. The body weights during these periods ranged from 3.7 kg. to 7.6 kg.

TABLE 2. METABOLISM OF NORMAL GEESE AT 10° TO 12° C. FASTED 24 TO 30 HOURS

Goose No. and date	Body Wt. Kg.	Previous Environmental Temp. °C.	Rectal Temp. at end of Exp. °C.	R.Q.	Heat Production per 24 hr.			Change from basal (22°C.) level %
					Total Cal.	Per Kg. Cal.	Per $10 \times W^{2/3}$	
104								
2/23/34	5.44	12	40.6	.71	279	51.2	902	− 5.8
109								
3/23/34	3.99	7	41.0	.72	274	68.7	1088	+17.2
111								
8/ 6/34	5.99	6	40.0	.73	398	66.5	1208	
8/15/34	5.98	8	40.3	.72	440	73.6	1336	
10/ 3/34	7.28	3	40.2	.75	528	72.6	1407	
10/ 8/34	7.16	4	40.6	.73	478	66.7	1286	
12/11/34	7.68	11	40.5	.74	542	70.5	1391	
2/ 5/35	7.78	10	41.2	.70	583	75.0	1486	
4/ 3/35	7.29	9	40.7	.72	545	74.8	1450	
4/30/35	7.18	10	40.6	.71	521	72.6	1400	
Average	7.04	8	40.5	.72	504	71.5	1370	+30.9
112								
7/18/34	5.86	8	41.4	.70	503	85.8	1547	
8/ 2/34	5.88	8	41.0	.70	449	76.4	1379	
8/ 8/34	5.63	7	41.1	.74	440	78.1	1388	
9/29/34	6.60	3	40.4	.71	403	61.1	1146	
10/ 6/34	6.14	3	40.9	.74	394	64.2	1175	
12/11/34	4.70	11	41.3	.72	341	72.5	1215	
1/31/35	5.96	9	41.2	.71	446	74.8	1357	
Average	5.82	7	41.0	.72	425	73.3	1315	+31.4
113								
8/13/34	4.36	7	40.4	.71	352	80.7	1319	
8/16/34	4.34	7	39.9	.70	299	68.8	1122	
10/ 1/34	5.01	1	39.7	.71	417	83.2	1424	
10/ 5/34	4.88	3	40.5	.70	362	74.0	1256	
10/ 9/34	4.89	4	39.9	.70	324	66.3	1125	
11/15/34	5.39	3	40.1	.70	415	76.9	1349	
12/18/34	5.33	11	41.5	.70	434	81.5	1423	
1/30/35	6.56	9	41.0	.70	539	82.2	1538	
Average	5.09	6	40.4	.70	393	76.7	1320	+41.3
114								
8/11/34	4.35	9	40.7	.73	352	81.0	1322	
8/14/34	4.24	7	40.7	.72	352	82.9	1342	
10/ 1/34	6.38	1	41.1	.73	387	60.7	1126	
10/ 5/34	6.20	3	41.3	.72	350	56.4	1037	
11/16/34	6.65	1	41.5	.70	402	60.4	1136	
12/10/34	6.69	10	41.5	.70	369	55.2	1040	
1/30/35	5.75	9	40.7	.73	303	52.6	943	
Average	5.75	6	41.1	.72	359	64.2	1135	+23.9
115								
4/ 8/35	4.09	9	41.1	.73	329	80.4	1286	+30.5
116								
4/ 9/35	5.37	8	40.5	.73	410	76.4	1337	+23.0
118								
4/ 2/35	4.63	9	41.4		272	58.8	979	
5/ 7/35	5.35	8	41.4	.70	335	62.6	1095	
5/28/35	5.98	10	41.5	.72	375	62.7	1130	
7/25/35	6.66	11	41.3	.70	548	82.2	1548	
3/12/36	6.86	12	41.1	.70	479	69.8	1326	
3/16/36	6.70	9		.70	444	69.2	1223	
Average	6.03	10	41.3	.70	409	67.6	1217	+30.9
Total Average	5.40		40.8	.72	376	70.0	1197	+24.8

The average heat production per kg. ranged from 51.4 to 68.8 calories per day with a total average of 58.4 calories. Calculated on the two-thirds power of the body weight, the minimal metabolism on any one day was 782 calories with goose *118*, and the maximum was 1231 calories with *112*. The average value for all of the animals was 994 calories. Four of the geese had basal values consistently above 1000 calories; 6 had levels rather consistently between 900 and 1000 calories. Thus the total average value of about 1000 calories gives a fair picture of the normal heat production at 22° to 24° C. in this group of geese. It should be noted, however, that treatment of the data by the method of analysis of variance shows that the 12 normal geese were inconsistent with respect to their basal metabolic levels and that this average value is valid only for this particular group. Within themselves, 7 of the geese, *104*, *108*, *109*, *110*, *111*, *113* and *116*, were consistent for different days. The other 5 showed significant shifts from day to day, for which no reason is yet apparent.

TABLE 3. METABOLISM OF THYROIDECTOMIZED GEESE AT DIFFERENT ENVIRONMENTAL TEMPERATURES

Goose No. and dates	Av. Body Wt. Kg.	Thyroid fed grains/ day	Av. Calories per 24 hr. per $10 \times W^{2/3}$			No. of experiments
			21°–24°C.	10°–12°C.	28°	
104♂						
3/16 to 4/26/34	4.93	None	701	1023		9
5/16 to 6/13/34	4.64	0.6	1008	1416		8
7/16/34 to 4/29/35	5.78	3.2	1071	1249	1228	19
3/ 4/36 to 3/24/36	5.26	None	766	1156	733	6
107♂						
2/10 to 3/ 1/34	4.69	None	683	993	659	4
108♀						
4/16 to 4/26/34	4.17	None	589	1047		3
5/16 to 6/20/34	4.38	1.0	881	1446		10
7/16 to 8/16/34	4.21	4.4	1119	1440		5
10/ 2 to 10/25/34	4.35	None	607	862	557	10
113♂						
3/28 to 6/ 5/35	4.33	None	687	990		8
Av., without thyroid treatment	4.62		672	1012	650	40

The respiratory quotient ranged from 0.69 to 0.74, with an average of 0.71. The rectal temperature at the end of the experiment from 40.7 to 42.2°C., with an average of 41.2°.

Table 2 shows the metabolic reactions of the normal geese to an environmental temperature of approximately 11°C. after being kept at this temperature for 24 hours. In 8 of the 9 geese there was a marked increase in metabolic rate, ranging from 17.2 to 41.3 per cent. In one animal no increase was observed, but, instead, a slight decrease from the basal level at 22°C. The average increase in the 9 geese amounted to 24.8 per cent. This represents 2 per cent or 20 calories per degree. The rectal temperatures averaged slightly lower than

those measured under an environmental temperature of 22°C. The respiratory quotients showed no significant change.

Treatment of the data for analysis of variance shows that at the temperature of 10° to 12°C. all of the geese showed significant shifts in their basal levels from day to day. Five of these did not show inconsistency from day to day, at temperatures of 21° to 24°C. Despite the individual heterogeneity, there is no question as to the increase in metabolism under cold conditions and the possibility is apparent that cold increases not only the level but also the variability of the heat production.

There was no obvious correlation of the metabolic response to a cold environment with the season of the year in which that variable was introduced. The conditions were such, however, as would be expected to diminish rather than to emphasize the operation of such a factor, since the animals were kept

TABLE 4. BODY TEMPERATURE

Condition	Environmental Temperature 22–24°C.	10–12°C.	16°C.	28°C.
Normal	41.2	40.8	40.9	42.0
Thyroidectomized	40.7	40.5		41.4
Thyroidectomized+thyroid feeding	41.2	41.0		42.4
Normal+thyroid feeding	41.3	40.9	41.1	41.6

under essentially uniform climatic conditions throughout the year—in the artificial climate of a building heated in winter and somewhat protected in summer. Except for 24-hour exposure to cold before experiments at 10° to 12°C., they were subjected less to cold than are most animals during a winter. The individual animal's variability from day to day is great enough to obscure the sharp definition of a possible seasonal factor unless a very large series of observations should be made over an extended period.

Metabolism after thyroidectomy. In table 3 are presented, in summary form, the measurements on 4 thyroidectomized geese at environmental temperatures of approximately 22°, 11° and 28°, together with measurements made during periods of thyroid feeding. The values represented the averages of 1 to 10 experiments on different days. After thyroidectomy in the 4 geese, the average basal level at 23°C. was 672 calories, a decrease of 33 per cent from the average normal level at the same temperature. This decrease is of about the same order as that observed in mammals after thyroidectomy. At an environmental temperature of 11°C., the thyroidectomized animals had an average level of 1012 calories, representing an increase of 50.6 per cent over their average level at 23°C., or 28.3 calories per degree. This is a relatively greater response than that of normal geese; the thyroidectomized geese were 33 per cent lower than the normals at 23°C. but only 15 per cent lower at 11°C. There is thus no question that the thyroidectomized goose can make metabolic adjustments to low temperatures, as great in magnitude as the normal animal.

The metabolic response to different dosages of thyroid gland was about what would be expected in the light of experience with mammals, that is, the metabolic effect does not vary directly with the dose, but with its logarithm. It

was desired to administer dosages in geese *104* and *108* that would bring their basal metabolism at 23°C. back to the preoperative normal level. This was accomplished by 0.6 grains per day in *104* and 1.0 grains per day in *108*. It was then desired to raise the basal level of metabolism in these animals by about 20 per cent over the normal level. The dosage of thyroid was increased gradually until a level of 3.2 grains per day for *104* and 4.4 grains per day for *108* was reached. The metabolic rate showed considerable resistance to change. The average level at the 3.2-grain dosage in *104* was only slightly above that at the 1.5-grain dosage; the level at 4.4-grain dosage in *108* was increased only 27 per cent over the level at the 1.0-grain dosage.

DISCUSSION

Starting with the work of Cramer in 1916, a considerable amount of histological evidence has been published, which has been generally interpreted as indicating an increased secretory activity in the thyroids of man and several of the rodents when exposed to cold environments. The findings are those of increased vascularity, cellular hypertrophy and hyperplasia, changes in the Golgi apparatus and mitochondria, and colloid withdrawal or accumulation. Kenyon (6) has recently reviewed evidence of increased thyroid activity in rats subjected to a temperature of —4° to +2°C. for 10 to 25 days.

Physiological evidence, as given by gland weight, calorigenesis and body temperature measurements, has been furnished by a number of workers. Riddle (3) has made a careful study of seasonal variations in the weight of the thyroid glands in pigeons, and has analyzed the similar published data of others on various species of mammals, mostly cattle, sheep and hog. He concludes that the thyroids of higher vertebrates respond promptly to autumn temperatures by enlargement, and to spring and summer temperatures by a decrease in size. These reponses are capable of being induced by the temperature alone. Riddle and Smith (9) also made the metabolic observations that feeding thyroid substance to doves kept at an environmental temperature of 15°C. decreases the normal rate of calorigenesis at that temperature.

Landauer (8), on the basis of metabolic evidence, considers that the frizzle fowl exhibits normally a physiological hyperthyroidism in an attempt, only partially successful, to compensate for the excessive rate of heat loss. Bodansky (17) has shown that the survival period of thyrotoxic rats is markedly influenced by the environmental temperature. At 4° to 6°C. they are much more resistant than at 20°C. He also showed that the hyperplasia and loss of colloid in the thyroids of normal rats exposed to cold can be prevented by the feeding of desiccated thyroid. Draize and Tatum (18) have shown that feeding of thyroid to rabbits at 33°C. is more toxic than at normal temperature of 20 to 25°C.

The essential evidence for the indispensability of the thyroid gland for thermogenesis in adaptation to a cold environment would be given by a demonstration of the failure of the mechanism after thyroidectomy. This has not been forthcoming. Indeed, the sum of the present evidence, much of it inconclusive by itself, is that the presence of the thyroid is not necessary for this calorigenic

response. The data of this paper show clearly that in the thyroidectomized goose there is an increased calorigenesis in response to a cold environment and that this may be as great in magnitude as in the normal animal.

This, of course, does not controvert the evidence cited above that the thyroid normally plays a part in the adaptive regulation of thermogenesis in changing environmental temperatures. The suspicion is well-grounded that such control is of an endocrine nature rather than through the nervous system, because of the time relations involved. There are some indications that the adrenal cortex may be an indispensable part of the regulatory mechanism. Adrenalectomized animals, and those with only the cortex removed, are abnormally affected by cold and succumb when exposed to temperatures that are easily tolerated by normal animals. They also have a low body temperature and a tendency towards a low basal metabolic rate. When placed for short periods of time in temperatures of 10°C. their basal metabolism is only slightly increased (19, 20).

SUMMARY

Basal metabolic rates were determined on 12 geese at environmental temperatures of 23° and 11°C. At the lower temperature the B.M.R. was increased 25 per cent, on the average, over the basal rate at 23°C.

Four of the geese were thyroidectomized and their metabolism was again measured at temperatures of 23° and 11°C. At 23°C. their average B.M.R. was 33 per cent lower than before thyroidectomy. At 11°C. the metabolic rate was 15 per cent lower than before thyroidectomy. The thyroid gland is thus shown not to be essential in this animal for thermogenesis in adaptation to a cold environment, since metabolic adjustments are made which are as great in magnitude as those made by normal animals.

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THE EFFECT OF HYPOGLYCEMIA ON THE METABOLISM OF THE BRAIN[1]

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The brain in its metabolic requirements is unique among organs. The available data indicate that the brain is the only organ to acquire its energy from the exclusive oxidation of carbohydrate. The evidence for this lies chiefly in the observation that the respiratory quotient of the brain *in situ* is unity (1, 2). The brain, moreover, has but little store of carbohydrate (3), hence, the fact that it absorbs both glucose and lactic acid from the cerebral blood (1, 4) is in conformity with the respiratory quotient of unity. Even in diabetes the respiratory quotient remains unchanged (1, 2). Furthermore, there is no evidence that fat enters into the respiratory metabolism of the brain, for acetone substances are neither poured into the bloodstream during diabetes, nor absorbed for oxidation from ketonemic blood traversing the brain (5). In an organ so dependent on carbohydrate and, indeed, the carbohydrate of the blood, hypoglycemia may have deep-seated results. The present investigation is an attempt to determine the effects of hypoglycemia on the metabolism of the brain. Such studies, moreover, may throw light on the mechanism of the response of the patient with schizophrenia to insulin injections.

METHOD

Methods previously described which involve a study of the arterial-venous exchange of organs were used (2, 6, 7). Cerebral blood samples were drawn from the superior longitudinal sinus and the arterial samples from the femoral artery. To compare effects of hypoglycemia on brain and muscle, venous blood was also collected from the femoral vein. The blood samples were analyzed for oxygen, carbon dioxide (8) and lactic acid (9). Non-fermentable (10) and total reducing substances (11) were also determined, using larger aliquots of the samples drawn during hypoglycemia.

The observations, which were made on fasted dogs, may be divided into two groups; in the first, the effects of hypoglycemia were studied, and in the second, those produced by the reversal of hypoglycemia following the intravenous injection of glucose.

First group. Production of hypoglycemia. Animals, 2 days post-absorptive, were injected with protamine-zinc insulin,[2] 1 U per kilo. On the third day without any further injection of insulin the animals were amytalized and the

[1] This investigation was aided by a Grant from the Child Neurology Research.
[2] We are grateful to Eli Lilly and Company for generous supplies of insulin.

superior longitudinal sinus and femoral vessels were exposed. After blood samples were collected standard insulin,[2] 1 U per kilo, was injected every 2 hours until both respiration and heart rate slowed markedly. The diminished heart rate, however, was taken as a criterion of the condition of the animals, as well as that of the metabolism of the brain. Usually the heart rate is approximately 160 per minute and this rate gradually decreases as the level of the blood sugar falls; first, slowly to about 100 per minute and then more rapidly to 70 per minute and lower, in one instance to 46 per minute. At this

TABLE 1. OXYGEN AND GLUCOSE EXCHANGE OF CEREBRAL BLOOD OF AMYTALIZED DOGS BEFORE HYPOGLYCEMIA.

Oxygen			Glucose[1]		
Arterial	Venous	Difference	Arterial	Venous	Difference
volumes per 100 cc.			mg. per 100 cc.		
19.06	12.37	7.67	88	77	11
14.01	8.99	5.02	89	87	2
14.77	8.87	5.90	86	76	10
19.90	9.70	10.20	62	52	10
19.06	10.42	8.54	99	76	23
17.90	9.32	8.58	110	90	20
20.19	9.67	10.50	95	78	17
17.35	9.28	8.07	79	61	18
21.59	11.78	9.81	82	75	7
23.68	9.23	14.45	74	51	23
24.21	9.32	14.89	74	67	7
18.79	9.91	8.88	76	67	9
17.70	9.15	8.55	82	63	19
19.56	12.73	6.83	100	89	11
17.14	5.79	11.35	83	68	15
16.14	7.55	8.59	73	66	7
Average		9.30	Average		13.1

[1] Total reducing substance.

time blood samples revealed a diminished cerebral exchange of glucose and oxygen.

Second group. Recovery from hypoglycemia. The preparations of these animals were the same as those of the first group but continued until the fourth day, when additional protamine-zinc insulin, 1 U per kilo, was given again but in 2 divided doses, a half in the morning and a half at night, thus ensuring a low level of blood sugar on the morning of the fifth day. At that time amytal was injected. Insulin was also administered, usually about 0.5 U. per kilo every 2 hours. The first samples of blood were collected when the heart rate had decreased to approximately 70 or less, then glucose was administered and the next series of blood samples were collected sometime after the heart rate had returned to normal. Other animals in this group were treated similarly but brought into deep coma by insulin and so could be studied without any narcotic. The blood vessels were exposed and samples of blood were drawn during and after recovery from hypoglycemic coma.

RESULTS

Sixteen observations of the normal cerebral exchange of 14 amytalized dogs (table 1) were made before insulin was injected. The average glucose

utilization was 13.1 mg. per cent, and that of oxygen 9.30 volumes per cent.

The results obtained after injection of insulin are presented in tables 2 and 3. With blood sugar values between 46 and 25 mg. per cent (table 2), 11 determinations on 9 animals reveal an average glucose uptake of 12.5 mg. per cent, and of oxygen 7.99 volumes per cent. During the more intense hypoglycemia (when arterial blood sugar was 22 to 7 mg. per cent), in 11 observations on 10 amytalized animals (table 3) utilization of glucose by the brain was reduced to 3.0 mg. per cent, and that of oxygen to 3.80 volumes per cent.

TABLE 2. GLUCOSE AND OXYGEN EXCHANGES OF CEREBRAL BLOOD OF AMYTALIZED DOGS DURING MODERATE HYPOGLYCEMIA.[1]

Arterial Blood Sugar mg. %	Utilization	
	Glucose mg. %	O_2 vol. %
25	9	11.41
42	32	10.21
46	29	7.75
26	7	4.87
37	13	9.42
27	12	11.07
28	1	9.18
33	9	7.69
28	4	3.77
34	11	6.48
26	10	6.05
	Average 12.5	7.99

[1] Total reducing substances between 46 and 25 mg. %.

Six observations were made on the effects of recovery from hypoglycemia 4 times in 3 amytalized dogs and once each in 2 dogs under no narcotic. The average oxygen uptake increased from 3.57 volumes per cent to 9.14 volumes per cent. In table 4 are presented the results of an amytalized dog subjected twice to hypoglycemia and recovery. During hypoglycemia no fermentable reducing substances are left in the blood and lactic acid values are not raised.

Table 5 reveals the exchanges of muscle. Before insulin was injected, the average utilization of glucose in 10 animals was 7.6 mg. per cent, and that of oxygen 6.91 volumes per cent. During hypoglycemia, on the other hand, the averages of 13 observations of these same animals revealed that the utilization of glucose had been reduced to 1.7 mg. per cent, although the average oxygen consumption of 6.04 volumes per cent was not significantly altered.

DISCUSSION

Normal fluctuations of utilization of glucose and oxygen. The present experiments reveal an average glucose uptake for the brain of 13.1 mg. per cent with arterial blood sugar varying between 110 and 62 mg. per cent (table 1). When the blood sugar begins to fall to lower levels, 42 to 26 mg. per cent, as a result of injections of insulin, the average glucose uptake in 10 observations remains the same, 12.5 mg. per cent (table 2). Presumably, most of the glucose so removed is used for oxidations. However, when blood sugar levels

are rapidly rising the brain is apt to absorb greater amounts of glucose than are necessary for oxidations. In a previous series of observations (1) in which blood sugar was raised to various values up to 245 mg. per cent as the result of experimental procedures, the average uptake in 22 observations was 23.5 mg. per cent. The additional glucose absorbed remains in solution in the tissue fluids and is not necessarily oxidized nor stored as glycogen. Probably an equilibrium exists in the glucose concentrations of the various body fluids. The additional amount of glucose absorbed, *i.e.*, the difference between 23.5 and 13.1 mg. per cent, represents the amount necessary for the maintenance of the equilibrium between glucose of the blood and that of the cerebral tissue fluids. That this is so can be seen by the fact that in the reverse condition when, after an initial high value blood sugar falls rapidly, the brain reverses

TABLE 3. GLUCOSE AND OXYGEN EXCHANGES OF CEREBRAL BLOOD OF AMYTALIZED DOGS DURING INTENSE HYPOGLYCEMIA.[1]

Glucose[2]			Oxygen		
Arterial	Venous	Difference	Arterial	Venous	Difference
mg. per 100 cc.			volumes per 100 cc.		
14	14	0	21.89	16.40	5.47
19	15	4	19.33	12.86	6.49
17	16	1	15.43	13.36	2.17
15	12	3	14.71	13.06	1.65
13	14	1	19.30	18.23	1.07
17	13	4	19.13	15.30	3.83
15	9	6	20.90	16.57	4.33
19	14	5	26.75	20.94	5.81
22	19	3	26.99	21.53	5.46
13	7	6	16.36	12.56	3.80
7	5	2	23.66	21.97	1.71
	Average	3.0			3.80

[1] Total reducing substances between 22 and 7 mg. %.

the usual glucose balance. Instead of absorbing glucose from the blood, the brain pours that substance back into the blood stream. This reversal may be seen following an injection of glucose and insulin when a sudden increase of blood sugar is followed by a rapid fall. Seven of the 11 significant observations made during the fall revealed a greater concentration of glucose in the venous than in the arterial blood, the increase of the venous concentration over the arterial varying between 5 and 36 mg. per cent. Such a reversal is presented in table 4 during recovery following the production of hypoglycemia for the second time in the same animal. It should be noted that the above glucose values refer to total reducing substances in the blood, but that about 7 mg. per cent should be subtracted for non-fermentable reducing substances. An average value of 7 mg. per cent of non-fermentable reducing substances was obtained after the blood was permitted to glycolyze.

The metabolic effects of glucose deprivation are reversible at any level of blood sugar if the animal is still capable of adequate respiratory and cardiac movements. For example, the resting oxygen consumption is 9.3 volumes per cent and, after the effects of hypoglycemia are reversed by intravenous glucose

injections, 9.14 volumes per cent. These values compare well with the averages of previous observations (2), which are 10.99, 9.99 and 9.4 volumes per cent for amytalized and unanesthetized, phlorhizinized and depancreatized dogs, respectively. Thus, while the cerebral absorption of glucose may vary during a rapid rise or the succeeding fall of that substance in the blood stream, the cerebral oxygen consumption remains constant even during these fluctuations of blood sugar. These results make the diminution of oxygen consumption during hypoglycemia all the more significant.

The lactic acid exchanges of the brain did not assume importance in the amytalized animals. The narcotic prevents the convulsions usually attendant on hypoglycemia. With this cause of a lactacidemia removed, the large doses of insulin do not increase blood lactic acid (12), but following the injection of glucose there is frequently an appreciable rise in lactic acid (13) (table 4).

TABLE 4. GLUCOSE AND OXYGEN EXCHANGE OF AN AMYTALIZED DOG SUBJECTED TWICE TO HYPOGLYCEMIA AND RECOVERY.

Time	Oxygen vol. %	Difference	Glucose Mg. %	Difference	Non-fermentable	Lactic Acid Mg. %	Heart Rate
A.M.							
9:40 Arterial	20.13		7		8	12	72
Venous	18.06	2.07	6	1	6	8	
9:43	*Injection of 25 gm. glucose*						
10:15 Arterial	21.30		89		7	28	162
Venous	12.24	9.06	84	5	7	20	
P.M.							
12:45 Arterial	26.05		7		6	15	66
Venous	23.02	3.03	6	1	5	lost	
1:05	*Injection of 40 gm. glucose*						
1:47 Arterial	22.58		98		8	22	160
Venous	13.46	9.12	106	−8	7	23	

Changes of glucose and oxygen utilization produced by hypoglycemia and recovery. At any level of arterial blood sugar between 25 and 245 mg. per cent the oxygen consumption of the brain remains essentially unchanged. However, when blood sugar falls to values between 22 and 7 mg. per cent and is maintained at these low values for some time, usually a matter of 1 or more hours, a distinct difference is observed in the venous blood of the brain, which assumes an arterial appearance. At these levels the glucose uptake of the brain is diminished below the usual utilization of approximately 13 mg. per cent and, therefore, becomes inadequate for the cerebral energetic requirements. The lack of supply of foodstuff is most evident at the level of 7 mg. per cent, which value includes no fermentable reducing substances.

If the diminished oxygen consumption of the brain is caused by lack of blood glucose, then, upon intravenous administration of glucose the metabolism of the brain should be increased to the normal level. As shown in table 4, on injection of glucose a greater oxygen consumption is reëstablished. This result is the counterpart of the diminished oxygen uptake during hypoglycemia and affords additional evidence for the conception that the oxidation of carbohydrate is the chief, if not the sole source of energy of the brain.

The above results were obtained on amytalized animals. However, in order to simulate the hypoglycemic treatment of schizophrenia, animals were also studied without a narcotic, but after they had been rendered comatose by the injection of insulin. In one such animal the oxygen uptake increased from 4.41 to 7.24 volumes per cent after the injection of glucose. The results are essentially unchanged, indicating that the narcotic is not a significant factor in the production of the cerebral metabolic changes. However, without the narcotic it was more difficult to produce a hypoglycemia of 22 mg. per cent or less. The convulsions which occur in the absence of a narcotic cause the breakdown of any remaining muscle glycogen (14) to lactic acid, which is then

TABLE 5. GLUCOSE AND OXYGEN EXCHANGES OF MUSCLE BEFORE AND AFTER HYPOGLYCEMIA.

Arterial Blood Sugar mg. %	Before Difference	O_2 vol. %	Arterial Blood Sugar mg. %	After Difference	O_2 vol. %
62	12	7.98	25	6	8.37
99	14	7.32	17	1	3.09
110	10	6.97	15	2	9.66
95	10	2.04	19	2	7.71
79	5	8.07	22	10	11.27
76	3	10.61	13	0	5.20
82	6	9.72	26	4	5.65
100	9	4.84	17	−1	1.24
83	7	5.91	27	3	4.73
73	0	5.60	33	1	6.02
			28	3	5.41
			34	0	7.14
			26	−9	3.01
Average	7.6	6.91		1.70	6.04

made available by the liver as blood sugar (15). This action is accelerated by increased activity of the adrenal medulla and sympathetic nervous system to mobilize muscle and liver glycogen (16, 17), an activity depressed by barbiturates. Despite the counteracting effects of these blood sugar-raising mechanisms, with continued administration of insulin it was possible to reproduce in 2 of 5 unanesthetized dogs results obtained in the amytalized animals.

Muscle. It is of interest to contrast the results obtained on brain with those on muscle. In the latter organ, oxygen consumption does not diminish when the glucose concentration of the blood does. The maintenance of the metabolic rate of muscle is due in part to its larger intrinsic store of glycogen. The brain contains only 0.1 per cent glycogen (3), while muscle may have 10 times as much. However, fasting, insulin and amytal (14) all combine to diminish muscle glycogen. It is, therefore, important to consider another factor, namely, the ability of muscle to oxidize fat. Observations on resting (6) and exercising (7) muscle reveal that both fat and carbohydrate may be oxidized and that diabetic muscle (18, 19) gets most, if not all of its energy from the oxidation of fat. Thus muscle, because of its ability to oxidize fat, in contrast with brain, maintains oxidations unaltered, despite the relative absence of carbohydrate. The depressant effect of an excess of insulin is specific

and can be exerted only on those tissues which oxidize carbohydrate exclusively.

Circulatory changes. The utilization of glucose and oxygen per 100 cc. of blood must necessarily change with the rate of blood flow through the brain, a more rapid flow bringing about a diminished exchange per 100 cc. of blood. Moreover, during hypoglycemia an increased minute volume of the heart has been observed (20). However, in the present experiments, due to a more intense hypoglycemia involving vagus overactivity, it is probable that the decreased exchange occurred despite a slower circulation. The fact that the heart rate is reduced to 50 or 25 per cent of its normal value undoubtedly makes for a diminished circulatory rate through the brain.

The slow heart rate is a manifestation of increased parasympathetic activity which ceases with the injection of atropine. Among other signs of parasympathetic activity observed during hypoglycemia, particularly in unamytalized dogs, is salivation. The slow heart rate, which is probably caused by increased irritability of the vagus centers in the medulla, is a signal of inadequate metabolism of the brain. It occurs usually with a diminished cerebral utilization of glucose and oxygen and, unless glucose is injected at this time, the animal succumbs to the hypoglycemia with a cessation of respiration.

The fall in heart rate, however, is not an infallible indicator of the diminished metabolic rate of the brain. It is well known that the sympathetic system which accelerates the heart is also active during hypoglycemia and occasionally after an early partial fall the sympathetic effects overcome those of the vagus and the heart becomes more rapid again. When this occurs, the cardiac criterion is lost and the animal may die of respiratory failure before it is known that the central nervous system is bereft of its necessary carbohydrate. Respiration, which becomes progressively slower, probably a direct effect of low blood sugar on the respiratory centers, ceases completely. However, such fatal eventualities may be obviated by proper preparation of the animal, which includes subjecting the dog to protamine-zinc insulin for at least 1 or 2 days before the observations are begun.

Cerebral metabolism during hypoglycemia. Even in profound hypoglycemia the brain is capable of a small oxygen consumption for a limited period. It is difficult to attribute this metabolism to the combustion of fat. Despite the large proportion of lipoid material of the brain, there has been as yet no evidence that this material plays a part in oxidation. The amounts of lactic acid absorbed by the brain cannot be large, probably due to the low concentration of lactic acid observed in the blood of amytalized dogs during intense hypoglycemia. Despite the low blood sugar in many experiments some small residual absorption of glucose continues. It is significant that with post-absorptive levels of blood sugar, the utilization of glucose, mg. per cent, and of oxygen, volumes per cent, approaches stoichiometric proportions, 4:3. However, with blood sugar values of 22 mg. per cent the ratio is reversed and the average utilization of glucose is less than that of oxygen. The store of carbohydrate in the brain, though small, is utilized during intense hypoglycemia (3) and, therefore, probably supplies the materials for oxidations. The fact that hypoglycemia is maintained for some time before oxygen consumption falls may also be attributed to intrinsic cerebral carbohydrate. It is proba-

ble that the central nervous system ceases to function only when no further carbohydrate, either in the blood or in the brain, is available for oxidation.

In a later paper we shall discuss the relationship between these observations and the hypoglycemic treatment of schizophrenia. At the present time, however, it is obvious that in the absence of glucose the diminished consumption of the brain reveals that that organ is deprived of its chief source of energy. The brain temporarily is suffering from a reduced ration. Its energetic requirements for the maintenance of normal function are diminished. Such changes have deep-seated effects on cerebral physiology.

SUMMARY

The effects of hypoglycemia on the glucose and oxygen exchanges of brain and muscle were studied in 29 dogs. The cerebral exchanges varied with the level of the blood sugar. With arterial blood sugar (total reducing substances) between 110 and 62 mg. per cent, the glucose utilization was 13.1 mg. per cent and that of oxygen 9.3 volumes per cent; with blood sugar values between 46 and 25 mg. per cent, the uptakes of glucose and oxygen were 12.5 mg. per cent and 7.99 volumes per cent respectively, but when blood sugar was reduced to values of 22 to 7 mg. per cent (nonfermentable reducing substances equal 7 mg. per cent), the glucose absorption decreased to 3.0 mg. per cent and that of oxygen to 3.8 volumes per cent. The intravenous injection of glucose during hypoglycemia restored the oxygen consumption of the brain to 9.14 volumes per cent. These observations are in marked contrast with those obtained simultaneously on the same animals but on another organ, namely, muscle. When the glucose utilization fell from 7.6 mg. per cent to 1.7 mg. per cent during hypoglycemia, the oxygen values were 6.91 volumes per cent and 6.04 volumes per cent respectively; not a significant change.

Addendum. After this paper was submitted for publication our attention was called to the observations of Dameshek, Myerson and Stephenson (Arch. Neurol. & Psychiat. **33:** 1. 1935) who have noted a diminished utilization of glucose and oxygen during insulin hypoglycemia in human subjects.

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THE EFFECT OF SPLENECTOMY ON THE WEIGHT OF THE HYPOPHYSIS OF THE ALBINO RAT

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The initial stimulus for the present study was a report by Waugh (1) on a female patient who had been splenectomized for thrombocytopenia 4 years prior to necropsy. Autopsy of this patient disclosed the following: hypertrichosis of the lip, chin and extremities; moderately enlarged thyroid with several large acini having atrophic lining cells and filled with colloid; a small cortical adenoma of the adrenal and a hypertrophied pituitary which was "about double normal size" due to hyperplasia of the chromophobe cells. This author mentioned that he had observed increased prominence of hair at least twice before on girls who had been splenectomized for thrombocytopenia. Moreover he pointed out that such a change is not uncommon in hyperplasia of the pituitary and stated that the present case "suggests that the removal of the spleen may be the initiating cause of the hypophyseal overgrowth."

It is of interest, in view of Waugh's findings and suggestion, to investigate the effect of splenectomy on the size of the hypophysis in some experimental animal. Accordingly 50 female albino rats of various ages were splenectomized under ether anesthesia and aseptic operative procedure. The operated animals were killed 2 weeks following splenectomy at which time their female litter mates were also sacrificed for controls. The body and hypophysis weights were recorded for both operated and control animals immediately following death and the hypophyses were placed in fixative for future histological examination.

In figure 1 are shown distribution curves of the weights of the hypophyses of the operated (*op*) and control (*co*) animals with histograms showing the mean ($\overline{X}$) weights of the hypophyses. It can be seen from this chart that the mean weight of the hypophyses of the 50 splenectomized animals is almost 8 mg. (.007796) whereas that of the 50 control animals is approximately 6 mg. (.005962), the latter being 25 per cent less than the former.

In order to test whether or not this mean difference is significant or likely attributable to random sampling, the data were treated according to the following statistical formulae:

(1) σ^2 (square of standard deviation) $= \dfrac{SX^2 - (SX)\,\overline{X}}{N}$

(2) $\sigma_{\overline{X}_1 - \overline{X}_2}$ (standard deviation of mean difference) $=$

$$\sqrt{\frac{X_1^2 + \sigma X_2^2}{N}}$$

[1] Waugh, T. R.: Folia Haematologica 48: 248. 1932.

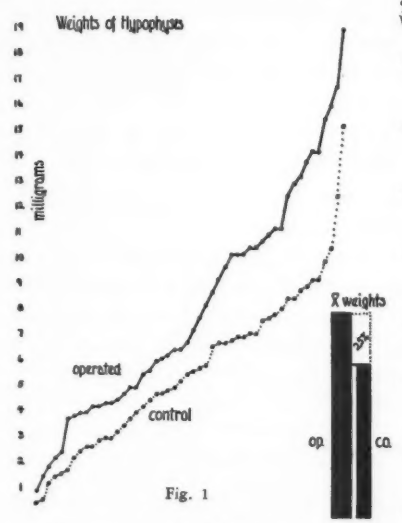

Fig. 1

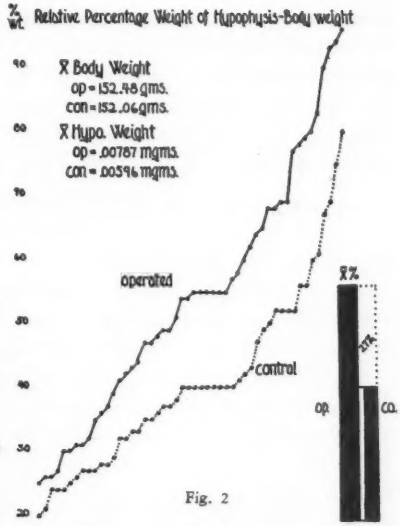

Fig. 2

Fig. 1. Chart showing distribution curves of the weights of the hypophyses, in mg., of the operated (*op*) and control (*co*) animals, and histograms showing the mean weights of the hypophyses of the (*op*) and control (*co*) animals.

Fig. 2. Chart showing distribution curves of the relative percentage weight of the hypophysis to the body weight of the operated and control animals, and histograms showing the mean relative percentage weight of hypophysis to body weight of the operated (*op*) and control (*co*) animals.

(3) $\dfrac{\overline{X}_1 - \overline{X}_2}{\sigma\overline{X}_1 - \overline{X}_2}$ = Normal deviation or probability ratio in which SX equals the sum of the hypophysis weights, $\overline{X}$ the mean weight and N the number of weights or hypophyses. X_1 refers to the operated and X_2 to the control group.

TABLE 1. STATISTICAL RESULTS OF HYPOPHYSIS WEIGHTS

	Splenectomized	Control
SX	3893	2981
SX^2	.00414418	.00229562
$\overline{X}$	.007796	.005962
σ^2	.000020687	.000010367
$\overline{X}_1 - \overline{X}_2 =$	.001834	
$\sigma\overline{X}_1 - \overline{X}_2 =$	.000787	
$\dfrac{\overline{X}_1 - \overline{X}_2}{\sigma\overline{X}_1 - \overline{X}_2} =$	2.33036	

When the probability ratio is compared with Fisher's table of probabilities the fact is brought out that the difference between the mean weights of the hypophyses of the splenectomized and control animals is significant and is not due to random sampling.

The next step was to determine the relative percentage of the hypophysis weight to the body weight. The distribution curves of these percentages and the histograms of the mean value for both operated and control animals are

shown in figure 2. Here again it can be observed that the difference between the mean values of the relative percentage weights of the operated and control groups amounts to 27 per cent, the mean of the operated group being 0.555 per cent and that of the control group being 0.404 per cent. Moreover, as shown on the chart, the mean body weights of the two groups are essentially similar. In table 2 is summarized the statistical treatment of these data.

TABLE 2. STATISTICAL RESULTS OF RELATIVE PERCENTAGE OF HYPOPHYSIS WEIGHT TO BODY WEIGHT

	Splenectomized	Control
SX	27.75	20.20
SX^2	17.39	9.967
$\overline{X}$	0.555	0.404
σ^2	0.03978	0.03612

$$\overline{X}_1 - \overline{X}_2 = .151$$

$$\sigma_{\overline{X}_1 - \overline{X}_2} = .03896$$

$$\frac{\overline{X}_1 - \overline{X}_2}{\sigma_{\overline{X}_1 - \overline{X}_2}} = 3.876$$

When the probability ratio is compared with Fisher's table of probabilities the fact is again brought out that the difference between the mean values of the relative percentage of hypophysis weight to body weight of the splenectomized and control animals is highly significant and not due to random sampling.

In order to determine whether or not splenectomy would likely affect the body weight of the operated animals during the post-operative period as compared with their controls both groups were weighed at the time of operation of the former group and at the time of death of both groups. In table 3 are recorded the results obtained in this phase of the study, B indicating the body weight at time of operation and A the weight at time of cancellation.

TABLE 3. MEAN BODY WEIGHTS OF ALBINO RATS

	Splenectomized		Control	
	A	B	A	B
$\overline{X}$	148.66 gm.	152.48 gm.	145.98 gm.	152.06 gm.
SX	7433 gm.	7624 gm.	7299 gm.	7603 gm.
+		3.82 gm.		7.08 gm.

In order to determine the probability for homogeneity in these groups of samples the chi square test was applied to these data, that is,

$$X_2 = \frac{\frac{SI}{SD}\left[SI\left(S\frac{D^2}{I}\right) - (SD)^2\right]}{SI - SD}$$

Here SI equals the sum of the body weights taken at the time of operation (B) and at the time of death (A) of both operated and control groups. Thus,

	B	A
$SI =$ Op	7299	7603 = 29959 gm.
Con	7433	7624

SD equals the sum of the body weights taken at the time of death (A) of both groups. Thus, $SD = 7603 + 7624 = 15227$ gm.

By the application of the above mentioned technique the probability for homogeneity was found to be approximately .46. Thus no significant difference existed between the mean body weights of the splenectomized and control animals at the time of cancellation.

It is evident from the data obtained in this study that removal of the spleen of the albino rat produces hypertrophy of the hypophysis. The question arises as to whether or not this effect is indicative of an endocrine function exhibited by the spleen or whether it is possibly attributable to a compensatory reaction of the reticulo-endothelial elements of the hypophysis resulting from the loss of the spleen. Further studies are in progress with the view to the solution of this problem. A preliminary histological examination of some of the hypophyses which were removed from the test animals seems to indicate that there is some evidence in support of both these views, that is, there appears to be an increased vascularity and an increase of the R-E cells as well as hyperplasia of the basophile cells, the latter being marked by numerous mitotic figures as many as 20 having been counted in one section of a gland and oftentimes as many as 3 appearing in one field.

Other phases of studies on the spleen which are now in progress concern such questions as the effect of splenectomy on the hypophysis of the male rat, the changes noted over various postoperative periods, the effect of splenic extracts on the hypophysis following splenectomy, physiological assays of the hypophyses of splenectomized animals and the effect of splenectomy on the gross and microscopic structure of the various endocrine glands, all with the view to determining the possibility of an endocrine factor in the spleen.

SUMMARY

The objective of this study was to determine the effect of splenectomy on the weight of the hypophysis. One hundred female albino rats of various ages were used, 50 of which were operated and 50 of which served for controls. The operation consisted of extirpation of the spleen under ether anesthesia and aseptic conditions by means of electric cautery. The post-operative period arbitrarily chosen between operation and cancellation was 2 weeks in all cases.

The mean hypophysis-weight of the operated animals was 25 per cent greater than that of the controls. The mean value of the relative percentage of hypophysis weight to body weight of the operated group was 27 per cent greater than that of the control group.

Statistical treatment of the data obtained in this study brings out the following facts. The difference in weight between the hypophysis of the splenectomized animals and that of the controls is significant and is not due to random sampling. The difference in body weight of the 2 groups of animals is not significant. The difference in the value of the relative percentage of the hypophysis weight to the body weight is significant.

Preliminary histological examination of some of the hypophyses removed from the operated animals seems to indicate an increased vascularity, an increase in the reticulo-endothelial cells, and hyperplasia of the basophile cells as evidenced by a marked increase in mitotic activity.

ALTERATIONS IN THE PERCENTAGE OF CELL TYPES IN THE HYPOPHYSIS BY GONAD TRANSPLANTATION IN THE RAT[1]

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An ovarian graft in the male rat, normal or castrated after puberty, produces only follicles, while both follicular development and luteinization occur in an ovary grafted into a female (1, 2). This has been interpreted on the basis of a physiological difference in the pituitaries of the two sexes (2). Cytological differences between the hypophyses of male and female rats were reported simultaneously by McQueen-Williams (3) and Wolfe and Ellison (4). When Pfeiffer (2) observed that the ovaries of females produced only follicles if testes had been grafted into the female at birth, he attributed this to an altered (masculinized) pituitary. Also ovaries transplanted at any time into rats castrated at birth, either male or female, produce both follicles and corpora lutea; but if a testis is present in the prepubertal period, only follicles are produced. This indicates an undifferentiated pituitary at birth which will differentiate according to the gonad present. The testis dominates this differentiation if both a testis and an ovary are present in the same individual.

All the above statements regarding the alteration of the pituitary are based upon physiological reactions. Therefore, the present investigation was undertaken in an attempt to correlate these physiological actions with the cytology of the pituitary and to demonstrate whether a pituitary which is experimentally altered in its physiological reactions shows corresponding changes in cell types. Also, since a number of castrated animals were used in these experiments, an opportunity was offered for further study of the ability of the grafted gonad to restore the normal cytology of the pituitary.

MATERIAL AND METHODS

Albino rats were used in all experiments. Castrations and transplantations of gonads into the newborn were done according to the technique of Pfeiffer (2), and grafting into the eye was done by the method of Goodman (1). All operations were performed under deep anesthesia. The physiological effects of ovarian grafts in the males were measured by the metaplasia of the muscle and connective tissue of the seminal vesicles. The effect of the testis graft in the female was measured by the masculinization of the clitoris and the

[1] The coöperation of the Committee for Research in Problems of Sex, National Research Council, is acknowledged with appreciation. The author wishes to thank also Professor Robert M. Yerkes, Director of the Yale Laboratories of Primate Biology, and Professor Edgar Allen of the Anatomy Department of Yale School of Medicine for extending the facilities of their laboratories and for the many helpful suggestions for carrying out this investigation.

absence of corpora lutea in the ovaries if present. All transplants, gonads, and secondary sexual accessory glands were sectioned at 10μ and stained with Congo red and Delafield's hematoxylin. The pituitaries were fixed in Helly's fluid, cut in cross section at 7μ, and stained in modified Mallory's triple connective tissue stain.

Cell counts were computed by using a millimeter-square ocular micrometer and counting the cells in alternate squares of a comparable field in each 10th section. The number of squares counted in each pituitary varied somewhat due to differences in size of the pituitaries and variations in the plane of sectioning; but the number of squares counted in all cases represented a good random sample. Therefore, it is assumed that the cells counted in each individual pituitary is representative of the entire cell count. This makes it possible to evaluate the cell types in terms of the percentage of the total number of cells in each pituitary and from this to find the average percentage for each group.

EXPERIMENTAL RESULTS

Cell types of altered male pituitaries. Four males were castrated at birth and at puberty (90 days of age) received in the right eye an ovary from a 22-day-old female. The ovarian grafts took in all cases and produced enough estrin to double, and in one case triple, the weight of the seminal vesicles over that of the control castrates. This increase in weight was due to metaplasia of the connective tissue. All animals were autopsied at 261 days of age. Cell counts of the pituitaries gave an average of 9.3 per cent basophiles and 35.1 per cent eosinophiles for the group (table 1). The extremes were 6.2 to 12.3 per cent for basophiles and 32.6 to 37.1 per cent eosinophiles. The percentage of eosinophiles very nearly approaches that given by Ellison and Wolfe (5) for the normal female, but the number of basophiles is even slightly higher than in the normal male.

The estrin produced by the ovarian graft was sufficient to prevent the formation of castration cells in the pituitaries (fig. 1). However, the basophiles were greatly increased in number which indicates that the estrin within the system was not as high as in the normal female since an increase in the number of basophiles in the pituitary seems to be correlated with a lack of the sex hormones. This lack is undoubtedly due to the transplantation factors, as these ovarian grafts were not from littermates or even from the same inbred strain. This would account for the lessened activity of the grafted tissue (6). However, the ovarian grafts showed both follicular development and luteinization.

Ten other males were castrated at birth and received an ovarian graft in the neck region at the same time. A second ovary from a 22-day-old female was transplanted into the right eye of 5 of the animals in this group just before puberty (60 days of age). The grafts in the eyes took in all cases, and all but one of the grafts in the neck were functional at autopsy. This one non-functional graft had evidently been active to some extent before puberty but contained only stroma at autopsy. All animals were autopsied at about 220 days of age. The seminal vesicles in every case showed 200 to 300 per cent

increase in weight over the control castrates. Those animals which received a second ovarian graft had a greater increase in seminal vesicle weight than the others of the group. In one case the increase reached as much as 1000 per cent.

The ovarian grafts in the eyes, as well as those in the neck, produced both follicles and corpora lutea, indicating a cyclic production of estrin and a normal interrelation between ovary and pituitary. Cell counts of the pituitary in the case of the animals with the ovarian grafts at birth gave an average of 34.8 per cent eosinophiles and 4.2 per cent basophiles (extremes of 31.7

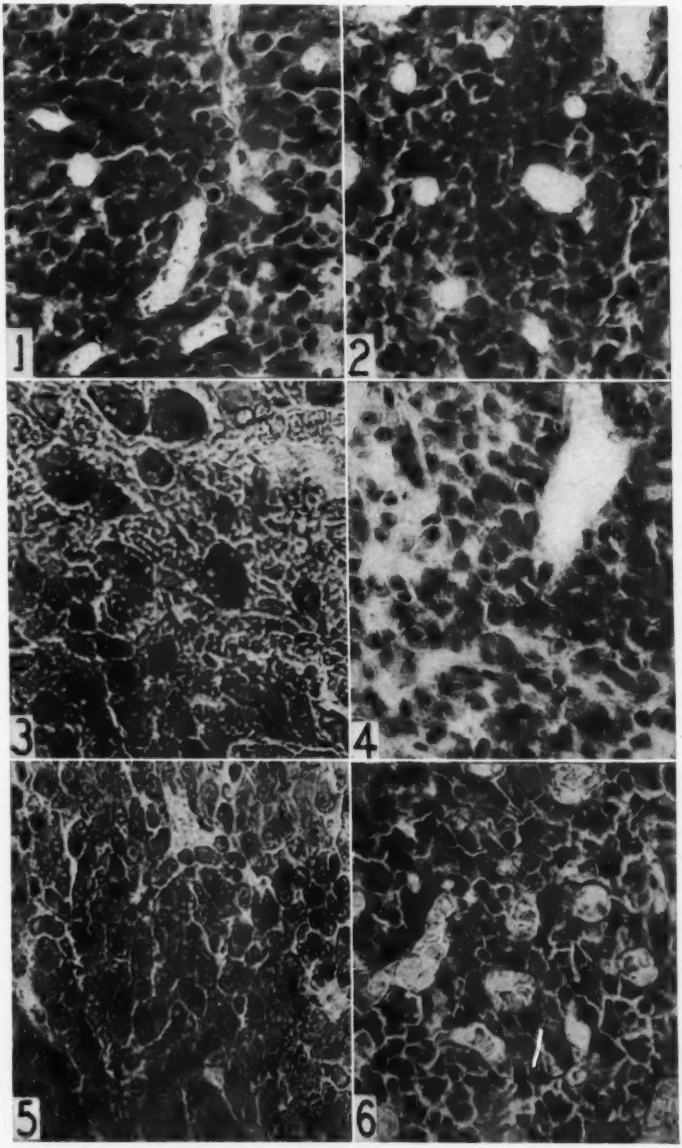
TABLE 1. CORRELATION OF THE PITUITARY CELL COUNTS WITH THE PHYSIOLOGICAL CHANGES INDUCED BY THE VARIOUS TYPES OF GONAD GRAFTING

No. of Rats	Genetical Sex	Time of Castration	Transplantation			Age at Autopsy	Condition of Graft	Seminal Vesicle Stimulation	Hormone Reactions	Hypophysis		
			tissue	condition	time of					baso-philes	eosino-philes	sex type
						days		by estrin		av.%	av.%	
4	♂	birth	ovary	22-day-old	puberty	261	foll. & corpora	+	cyclic	9.3	35.1	♀
5	♂	birth	ovary	22-day-old	puberty	220	foll. & corpora	++	cyclic	3.4	32.9	♀
5	♂	birth	ovary	newborn	birth	220	foll. & corpora	++	cyclic	4.2	34.8	♀
7	♂		ovary	newborn	birth	200	follicles	−+	non cyclic	8.4	53.9	♂
4	♂	birth	testis	newborn	birth	220	cryptorchid		non cyclic	8.1	51.7	♂
3	♂					220			non cyclic	6.0	52.3	♂
3	♂	puberty				220				12.1	52.3	♂
4	♀	birth	ovary	newborn	birth	200	foll. & corpora		cyclic	5.4	32.3	♀
4	♀	birth	ovary	22-day-old	puberty	200	foll. & corpora		cyclic	4.8	31.8	♀
8	♀	puberty	ovary	newborn	puberty	230–300	mainly follicles		non cyclic?	6.8	32.8	♀
4	♀	birth	testis	newborn	birth	200	cryptorchid		non cyclic	8.4	52.1	♂
11	♀		testis	newborn	birth	234–463	cryptorchid		non cyclic	5.2	51.4	♂
8	♀					260			cyclic	4.7	32.1	♀
2	♀	puberty				220				7.9[1]	39.2	♀

[1] 17.6% of basophiles and castrate cells.

to 37.1 and 3.2 to 8.4 per cent respectively). In the group that received a second ovary in the right eye at puberty there were 32.9 per cent eosinophiles and 3.4 per cent basophiles (table 1), (extremes of 30.8 to 36.7 and 3.1 to 3.7 per cent respectively). The increase in the percentage of basophiles in the first group is due to a single animal in which the graft at birth was not functional during the entire tenure of the experiment and would, therefore, classify this animal more nearly with that of an early castrate. It had a basophile count of 8.4 per cent which raised the average for the entire group from 3.8 to 4.2 per cent. However, low eosinophile count classifies it as having been altered to the female type. The cell counts of both of these groups very closely approximate that given by the normal female. There was no evidence of castrate cells or of an increase in the basophiles except in the single case mentioned above.

Since an ovarian graft in the male castrated at birth produces the female cell picture in the pituitary, it is then of interest to determine its effect in the normal male. Therefore, 7 normal males were grafted at birth with ovaries of newborn littermate females and were autopsied after 200 days. Ovarian grafts were recovered in all cases, but no corpora lutea were found in any of them, although there was good follicular development. Some estrin must have been present since the seminal vesicles, although normal in structure and secretory activity, showed a decided augmentation. This was probably due to the action of both estrin and male hormone (7). The cell counts of the pituitaries indicated a perfectly normal male condition (fig. 2) with an



All figures are photomicrographs of cross sections of anterior pituitary stained with a modified Mallory's triple connective tissue stain. Magnification X400.

1. Male rat castrated at birth and receiving an ovarian graft at puberty. Note the female distribution of eosinophiles and the absence of castrate cells.

2. Normal male carrying an ovarian graft from birth. Note that the cell distribution is distinctly male.

3. Male with its own testes transplanted to the neck region at birth (autotransplantation). Note the typical castrate cells.

4. Female with ovaries transferred to the neck region at birth and an ovarian graft in the eye at puberty. Unlike figure 5 there are no castrate cells, and the cell distribution is typically female.

5. Female castrated at birth and receiving a testis graft in the neck at the same time. At puberty an ovarian graft was placed in the eye. Note the typical male distribution of cells.

6. Normal female which received testes in the neck at birth and gave the characteristic constant estrus vaginal smear typical of this group. The cell picture is of the male type. Note the increased vascularity of the pituitary. This is very striking when the entire area of the pituitary is studied.

average of 8.4 per cent basophiles and 53.9 per cent eosinophiles (table 1). The extremes were 5.3 to 9.4 per cent in the former case and 51.1 to 57.2 per cent in the latter.

Since it seems evident that the testes, when in the normal position, control the differentiation of the pituitary, it becomes necessary to determine whether transplantation is a factor. Therefore, 4 newborn males had their testes removed from the normal position and transplanted to the neck region (autotransplants). The grafts took in all cases, but there was some variation in the physiological response of the animals. Spermatogenesis in the grafts varied from only a few spermatogonia in the tubules to tubules with possible secondary spermatocytes present. They were more highly developed than a cryptorchid testis after the same length of time. In no case were the grafts able to completely prevent castrate cells in the pituitary (fig. 3). However, the animals with the best testes grafts had only a few castrate cells present although the basophiles were increased in number. The seminal vesicles produced some secretion, but they were only about midway in size between the normal and the adult castrate condition. Cell counts of the pituitaries showed an average of 51.7 per cent eosinophiles and 8.1 per cent basophiles (extremes being 49.1 to 54.2 and 6.3 to 12.0 per cent respectively). This count is intermediate between that of the normal and the castrate type. At least it does not indicate any change toward the female type. It indicates that the testis, even in an atypical position, is able to cause the pituitary to differentiate in the male direction.

Three normal and 3 castrate males of similar age to those in the above experiments were used as controls. The average cell counts (table 1) of the normal males were 6.0 per cent basophiles and 52.3 per cent eosinophiles (extremes of 5.2 to 7.8 and 51.1 to 56.8 per cent respectively). The cell counts in the pituitaries of the castrate males were 12.1 per cent basophiles and 52.3 per cent eosinophiles (extremes 8.8 to 14.1 and 50.1 to 55.2 per cent respectively). These check so closely with the counts made by Wolfe and Phelps (8) that it was not thought necessary to increase the number of controls since they would have to be derived from animals which were not littermates of the groups used above.

Cell types of altered female pituitaries. Since the testis influences the differentiation of the genetical male pituitary, and since in the absence of the testis the ovary is able to cause the male pituitary to differentiate toward the female type, it is necessary to check the genetical female pituitary under the same circumstances. Therefore, 8 females were castrated at birth. Four received an ovarian graft in the eye at puberty, and 4 had their own ovaries placed in the neck region at birth (autotransplantation). The animals with the ovaries transferred to the neck region ran normal cycles for about 90 to 100 days after puberty. About this time the cycles became irregular and castrate cells appeared in the pituitaries (see also 2). The group with ovaries in the eye ran normal cycles coupled with the cyclic production of follicles and corpora lutea (also 2). At autopsy (200 days) the averages of the cell counts of the pituitaries were 4.8 per cent basophiles and 31.8 per cent eosinophiles for the second group, and 5.4 per cent basophiles and 32.3

per cent eosinophiles, with about 5 per cent castrate cells in the first group (table 1). These are the typical female conditions (fig. 4). The increase in basophiles and formation of castrate cells is directly correlated with the exhaustion of the ovarian transplants and has been shown to be due to transplantation factors (2).

Another group of 8 females were castrated shortly after puberty (85 days of age) and received in the kidneys at the same operation ovarian grafts from newborn females. The grafts took in all but one case. This single animal resembled in every way the typical castrate and was treated with that group. Cycles reappeared in 12 to 16 days and were normal except for a slight lengthening of their duration, until transplantation factors caused the degeneration of the grafts. The ability to form corpora lutea was lost first and finally follicular development became so weak that castrate cells appeared in the pituitaries. At autopsy (230 to 300 days of age) the histological picture of the hypophysis was that of the normal female except that there was a varied increase in the numbers of castrate cells and of enlarged basophiles. Cell counts gave an average of 32.8 per cent eosinophiles and 6.8 per cent basophiles with from 0 to 10 per cent castrate cells depending upon the condition of the ovarian graft. The ovarian graft is capable of giving the normal female picture in the pituitary regardless of the time of castration or age of the tissue grafted, provided a testis had not been present at some time in the development of the individual.

Pituitaries of females with testis grafts. If the testis prevents the grafted ovary from producing the female cell picture in the genetical male, it is necessary to determine whether the testis is capable of producing the cell picture of the male in the pituitary of the female (castrated or normal). Therefore, 4 females were castrated at birth and had testes from littermate males placed in the neck at the same time. The testes took in all cases and developed to the same stage as described above for the testis grafts in the castrated males. The females became definitely masculinized. The clitoris enlarged into a penis-like organ often extending beyond the dermal sack. Ovarian grafts placed in the eye after puberty responded with only follicular development as is typical in the male. The castrate cells which are present in the pituitary of a castrated animal bearing a testis graft disappear after the implantation of an ovary into the eye, but the rest of the pituitary picture remains about the same (fig. 5). The number of castrate cells here, as also in the case of the testis grafts in castrate males, depends upon the development of the graft. The average of the pituitary cell counts for the group (table 1) was 8.4 per cent basophiles and 52.1 per cent eosinophiles (extremes 6.8 to 12.1 and 48.8 to 57.6 per cent respectively). The increase in basophiles is due to a lack of equilibrium between the gonad grafts and the pituitary. However, except for this fact the picture is so nearly like that of the normal male that it may readily be concluded that the testis is capable of differentiating the pituitary in the male direction regardless of the genetic sex.

It was next necessary to determine the effect of the grafted testis in the female where the ovary is in its normal position and not subject to the destructive factors of grafting. From a group of females which had received

2 testes from littermate males in the neck at birth, 11 animals were chosen in which the grafts had taken sufficiently well to influence the pituitary. Animals of this type run a constant estrus vaginal smear, but the estrin level is at all times below that at normal estrus (2). In this case the host ovary responds identically with that of the ovarian graft in the male. It does not produce corpora lutea, although it is capable of doing so if luteinizing hormone is supplied. The animals were autopsied at from 234 to 463 days of age, after running constant estrus for 3 to 12 months. The average cell counts of the pituitaries for the group was 5.2 per cent basophiles and 51.4 per cent eosinophiles (table 1) with extremes of 4.5 to 8.3 and 47.3 to 58.4 per cent respectively. The cell distribution approximates that of the normal male (fig. 6) and demonstrates that the testis can differentiate the pituitary toward the male condition regardless of the genetical sex of the individual or whether an ovary is present or not.

Eight normal females in various phases of the estrus cycle and 2 castrates were used as controls. The average pituitary cell counts for the normals was 4.7 per cent basophiles and 32.1 per cent eosinophiles; for castrates 7.9 per cent basophiles (basophiles plus castrate cells 17.6 per cent) and eosinophiles 39.2 per cent.

DISCUSSION

An analysis of the data presented here definitely indicates that when the endocrine function of the gonads is altered, provided this alteration is permanent, there is a histological and cytological change in the pituitary which can be correlated with the physiology. Since a total of 121,951 cells were counted, the data seems reliable for the animals here investigated. The fact that the cell counts within each group fall more closely together than would be possible if the counts had been made from individuals selected at random from the entire number investigated, counteracts any error which might be expected due to the small number of animals used in certain groups.

Since the physiology of the experimental groups is often intermediate between the male and the female types, it is not surprising that the cell percentages in the upper extreme of one group closely approximate the lower limit of the next group. Thus, the experimental animals fall into a fairly continuous series rather than into two distinct groups corresponding to the sexes, as is the case in normal animals. However, if only the percentages of eosinophiles are considered, the two groupings appear, but the range in each group is wider than normal. That the basophiles do not show this division may be explained as due either to the castration factor or to the inability of the grafted gonad to reach a normal state of interaction with the pituitary. It has long been known (9, 10, 11, 5 and 12) that the first change in the rat pituitary after castration or the withdrawal of the sex hormones is the increase in the number of basophiles. This is also true when there is any interference with the gonads, as in cryptorchidism.

It has been definitely shown that male pituitaries have a greater gonad stimulating activity and a greater number of basophiles. In some cases a few enlarged basophiles (so-called castrate cells) may also be present (8 and the present investigation). These changes increase with damage to the testes

and reach their maximum upon castration, so it may be possible that the number of basophiles is determined solely by the amount of sex hormones present under the experimental conditions. These facts would make it extremely difficult to determine, in the case of an ovarian graft in the male that did not take very well, whether the pituitary condition found is due to the smaller quantity of sex hormones or whether it is due to the fact that the graft has not taken sufficiently to alter the male type. Also, in the case of females which have received testis grafts at birth, the increase of basophiles may be due to a lowered concentration of estrin in the blood, since it has been shown by Pfeiffer (2) that even though these females have constant estrus smears, it is really a sub-estrual condition. The eosinophiles on the other hand do not appear to be as dependent upon the level of the sex hormone, but are influenced rather by the presence of the specific gonad during the prepubertal stage. Therefore, if we consider the eosinophiles, it is quite easy to determine in which category the above cases belong.

There is some fluctuation of the eosinophiles which may be correlated with the physiology. This includes mainly a change in the granular content of the cytoplasm (13), but there may also be an actual change in the cell percentage. However, these variations appear to lie in definite limits within the sex type, and the cells do not change to the other sex type unless the pituitary is dominated by gonads of the opposite sex at such a time and over such a period of time as is necessary to alter its physiology. The granular changes were so difficult to determine in the present preparations (due to the thickness of the sections) that no attempt was made to count them or to correlate them with hormone function.

The investigations of the author (2) indicate that there are different sex patterns in the physiology of the pituitary which can be correlated with the cell patterns first described by Wolfe and Ellison (4) and McQueen-Williams (3). Wolfe (13) has shown that changes in the endocrine physiology are accompanied by variations in the histology and cytology of the pituitary. However, the present investigation indicates that these variations remain within the specific sex pattern, and while the histological picture may be altered at will within the limits of this pattern, the sex pattern itself cannot be readily changed once it has been fully established.

The alterations within the pattern consist of changes in granular content of the various cells and some change of chromophobes to basophiles or, less frequently, to eosinophiles, and vice versa. It is possible, then, that during the stage when there is great developmental activity (from birth to puberty), the pattern may be altered or laid down with respect to the stimulation of the gonad present. If a gonad is not present, either there is no definite pattern established, or the indifferent pattern is so close to the female type that it is capable of responding to a grafted ovary as though it were a normal female. In this connection it is of interest that Leblond[2] has observed that in the pituitary of the newborn rat the basophiles are not differentiated and only a few eosinophiles may be observed. However, toward the end of the second week a marked differentiation seems to occur so that at about 20 days

[2] Personal communication from Charles P. Leblond of the Anatomy Department of Yale University Medical School.

eosinophiles and basophiles have become both numerous and readily distinguishable. This is in agreement with the fact, observed by Pfeiffer (2 and the present investigation), that the pituitary of the rat is undifferentiated at birth and becomes differentiated under the influence of the gonads during the prepubertal stage.

SUMMARY AND CONCLUSIONS

Males castrated at birth and receiving ovaries in the neck at this time, or in the eye at puberty, have the female type of pituitary both in physiological response and in cell counts. This is especially true of the eosinophiles. However, the basophiles may vary a great deal with the state of the graft. Therefore, more consistent results are obtained if the animals are grafted both at birth and at puberty. The cell counts for the latter were 3.4 per cent basophiles and 32.9 per cent eosinophiles.

If females are castrated at birth and receive testis grafts at this time, the histological pattern of the pituitary after puberty is that of the male. Under the most favorable conditions the cell counts of the pituitaries are about 8.4 per cent basophiles and 52.1 per cent eosinophiles. Castrate cells are always present to a certain degree, although they are not nearly so numerous as in the cryptorchid animal. This is correlated with a better condition of the testis than is found in the cryptorchid of the same time interval.

Genetical females castrated either at birth or at puberty and grafted with ovaries produce the female cell pattern in the pituitary. Genetical males castrated at birth and grafted with testes have the male cell pattern in the pituitary. However, if both a testis and an ovary are present in the same animal, regardless of its genetical sex, the tendency is to form the male pattern.

The cell counts of the pituitaries of normal males receiving ovarian transplants at birth are 8.4 per cent basophiles and 53.9 per cent eosinophiles. The cell counts of the pituitaries of normal females which had received testes grafts at birth are 5.2 per cent basophiles and 51.4 per cent eosinophiles. Therefore, the testis has a greater influence upon the differentiation of the pituitary than does the ovary.

There is a definite pattern in the pituitary of the rat which is distinct for each sex. Each pattern is represented by characteristic percentages of cell types. Both the physiology and the histology may be altered within the limits of this pattern, but attempts to alter the pattern after the pituitary has become completely differentiated have thus far been unsuccessful.

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CURRENT ENDOCRINE LITERATURE

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BOOK REVIEWS

Exophthalmic Goiter and its Medical Treatment. Bram, Israel, Pp. 456, The C. V. Mosby Company, St. Louis, 1936.

The fact that this work has gone into a second edition speaks for itself. The author's purpose is to render available the results of many years of experience as an internist specializing in the treatment of Graves' disease, both to those who believe in the primary surgical treatment and those who prefer to utilize only the resources of the non-surgical practitioner in the treatment of the disorder. Bram's thesis is that exophthalmic goiter represents a constitutional malady and that thyroidectomy is at best a convenient palliative measure. In any case skilful management of the 'patient as a whole' is demanded and the factors entering into such management form the theme of the work.

The various chapters cover such topics as etiology, symptomatology and the differential diagnosis as well as treatment. Two of the most useful chapters are those dealing with drug therapy, including hormone preparations, and psychotherapy. In the latter, common-sense utilization of suggestion to bring about integration of the personality is chiefly relied upon; various ways of bringing it to bear are discussed.

The author summarizes his results in 2600 cases treated medically and personally followed up for 3 to 20 years as 90 per cent complete cures and with most of the remaining 10 per cent enjoying social and economic usefulness. The average time of absence from customary duties was about 14 weeks.

The book is readable and well-illustrated.

The Endocrines in Theory and Practice. Articles Republished from the British Medical Journal, Pp. 278, H. K. Lewis & Co., Ltd., London, 1937.

The book represents a collection of articles reprinted from the British Medical Journal. It consists of 28 chapters on such topics as "The problem of endemic goitre," "Physiology of the adrenal glands," "Hormone deficiencies in the male," etc. The collection has the obvious advantage of timeliness and of reflecting the attitudes and opinions of well-qualified contemporaries. It is practical and useful. It necessarily, however, lacks the unity and thoroughness of a more systematic treatise.

Autonomic Neuro-Effector Systems. Cannon, W. B., and A. Rosenblueth, Pp. 229, The Macmillan Co., New York, 1937.

The central interest in the preparation of this Monograph was, in the authors' words, "to render an organized account of recently acquired evidence regarding the

chemical step which intervenes between the nerve impulse and the effector in the functioning of the autonomic nervous system." The book deals primarily with the researches of the Harvard group, the historical aspects having been left largely to the surveys of Bacq and Gaddum. Parker's recent monograph on humeral transmission in the lower forms further obviated wide excursions. The book is of interest to Endocrinologists primarily in that it considers in a penetrating way the nexus of hormonal and neurological physiology. More particularly, the relationship between adrenin and sympathin is of immediate endocrine interest. The subject matter is treated in 14 chapters dealing with such matters as organization of the autonomic system, chemical mediation of nerve impulses, sympathetic and parasympathetic agents and their production under natural and experimental conditions.

Sympathin is regarded as a compound of adrenin with the receptor substances of the sympathetically innervated cells. These may give rise to either excitation or inhibition and correspondingly two compounds are postulated, namely sympathin E and sympathin I.

The authors recognize that their theoretical treatment of certain aspects of the subject may be regarded as over-elaborate or redundant. A considerable degree of ingenuity is displayed in harmonizing some of the cited evidence with the theory set forth. One wonders whether so much ingenuity would be required were more attention given to the recorded evidence of saturation of receptive substances, differential effector thresholds, and change of sign of reaction when either the quantity or duration of acting humoral agents is varied.

To those wishing to make contact with the recent evidence on the topics treated, the book will be indispensable. They will find it a challenging and stimulating treatise.

The book is well printed and illustrated with numerous graphs—largely original. It closes with a list of 344 pertinent references.

Der Endemische Kretinismus. De Quervain, F. and C. Wegelin, Pp. 500, Julius Springer, Berlin and Vienna, 1936.

This timely monograph by two authorities will be welcomed by all students of endocrinology. It is based upon the authors' extensive personal clinical and postmortem observations over many years in regions affording opportunities for the study of both endemic goiter and endemic cretinism. The historical background, epidemiology, clinical findings, pathological anatomy and physiology, pathogenesis, prophylaxis and treatment are considered in detail; De Quervain discussing the clinical and physiological problems and Wegelin the pathological. De Quervain emphasizes the confusion which exists between the conception of endemic cretinism and two other conditions, athyrosis and acquired infantile myxedema. He discusses the differential points in detail and concludes that there is no relationship between the latter two and endemic cretinism and advises that the term "sporadic cretinism" be discarded.

The situation in America is summed up by Wegelin in a short paragraph which will not be accepted by all as being factually correct. While he states that endemic goiter is not associated in this country with endemic cretinism, he quotes Jackson to the effect that there are about 1000 cases of "cretinism" in America. As the latter acknowledges that he does not differentiate between endemic and sporadic types, his statistics cannot be accepted as representing the incidence of true endemic cretinism according to the conception and definition of De Quervain. One is left with the impression that true endemic cretinism does not exist in America; and

furthermore that mental retardation in children in endemic goiter regions in this country is not related to either endemic goiter or endemic cretinism.

The authors discuss the beneficial results obtained by the prophylactic use of iodized salt, the therapeutic administration of desiccated thyroid and the operative management of the enlarged gland in goitrous cretins.

The book is well printed and profusely illustrated with photographs of patients, pathological material, and roentgenograms. It will be accepted as the latest authoritative word on the subject of endemic cretinism.

Practical Endocrinology. Symptoms and Treatment. Goldzieher, Max A., Pp. 344, D. Appleton-Century Company, Inc., New York, 2nd Ed., 1937.

The new edition of Goldzieher's well-known book preserves the desirable qualities of the first edition. It has been brought up to date by various minor changes in the main body of the text with a supplement of 14 pages for major items.

It is a practical book in the best sense of the term and makes easily available to the practitioner those parts of endocrine lore that are now applicable clinically. Enough of the experimental laboratory data are included for intelligent orientation.

Surgical Pathology of the Thyroid Gland. Hertzler, Arthur E., Pp. 298, J. B. Lippincott Company, Philadelphia, 1936.

This is a challenging book the conclusions of which go contrary to much that is conventionally believed by physiologists and surgeons. It represents an attempt to tell the truth, uncolored by tradition, as seen by a physician who has been privileged to study the life histories of many patients encountered in the practice of medicine in a stable Kansas community over a period of 40 years. Hertzler has studied his patients, removed their goiters, studied the glands in gross, and many slides stained with a great variety of dyes. He has "tried to write a continued story from these individual observations."

He believes that the evolution of thyroid surgery has been greatly over-influenced by "the Kocher fetish of cachexia thyropraevia." He regards total thryroidectomy in adults as commonly not only a harmless procedure but one at times even curative of myxedema. While recognizing the existence of true thyroprivic myxedema he believes that many cases are due, not to deficiency of thyroid secretion but to the action of a perverted secretion originating in degenerated thyroid tissue. He stresses as even more important than thyrotoxicosis as ordinarily conceived, a subtle cardiac degeneration due to this perverted secretion. To Hertzler there is no such thing as an 'innocent goiter' save the pre-puberal or puberal colloid type. All others should be transferred in toto to the specimen jar of the surgical pathologists. The patient may or may not need tiding over to readjustment by use of thyroid medication.

The book is written in a racy style. It is profusely illustrated by original photographs of patients and their thyroids in gross and in section. The evidence presented deserves the careful consideration of all thoughtful endocrinologists. Its perusal will prove to be a pleasure rather than a task. It refreshingly opens to new considerations what had become rather a stale subject.

The Endocrines in Obstetrics and Gynecology. Kurzrok, Raphael, Pp. 488, The Williams and Wilkins Company, Baltimore, 1937.

There is a particular need for this book. So rapid has been the advancement in the field of endocrinology as to render almost impossible to anyone except the closely attentive and experienced expert a critical appreciation of its clinical significance. While a respectable proportion of papers currently appearing are based

on clinical studies or on experimental work with the primates many of the fundamental features that are of interest to the gynecologist have been carried so far only through rodent experimentation. The author is particularly well-equipped to offer a critical evaluation of this literature. For years he has been a close student of the subject and has been a competent original investigator in both the clinical and experimental fields.

The book begins with a more than usually satisfactory historical introduction. This is followed by a chapter on the physiology of the female sex hormones, one on their chemistry and then a series of chapters on the individual endocrine glands. In the more strictly clinical section are included chapters on such subjects as menstruation, ovulation, pregnancy and their various pathological disturbances. The book closes with chapters on functional sterility, the male sex hormones and methods of hormone assay.

It is concisely and clearly written, well-illustrated and creditably printed. It should prove to be one of the most useful books in the library of the gynecologist and almost indispensable to one attempting to keep up-to-date in the fundamentals of that specialty. The internist will also find much of interest in the book.

League of Nations Quarterly Bulletin of the Health Organisation. Report of the Permanent Commission on Biological Standardisation. Special number, November 1936. Columbia University Press.

The problem of international standardization of insulin is treated in eleven chapters by various authorities. Comparisons of unit values of various standards is made and methods of assay are discussed.

Glandulas Sexuaes e Hypophyse Anterior. Martins, Thales, Pp. 543, Companhia Editora Nacional, São Paulo, 1936.

The book is based on work of recent years in the Oswaldo Cruz and Butantan Institutes. It affords to those able to read Portugese ready access to these researches in succint form. In addition, the more important of the classic and of recent researches are utilized for orientation. The book in its order of topics follows the conventional pattern: anatomical introduction, general biology, the hormones of the follicles and corpora lutea, etc., leading to a discussion of the various clinical aspects of the subject.

The book is clearly printed and fairly well illustrated.

The Practice of Medicine. Meakins, Jonathan Campbell, Pp. 1341, C. V. Mosby Co., 1936.

The book includes a 40-page discussion of diabetes mellitus in a section on "Diseases of Metabolism" and a 70-page treatment of the other endocrine disorders under designation of "Diseases of the Ductless Glands." Both sections were written by Dr. E. H. Mason.

From the standpoint of the endocrinologist, the book is of interest primarily as indicating the informational equipment recommended for the general practitioner in dealing with endocrine disorders. It is significant that the hormonal disorders bulk proportionately so large in the total field.

The readers will find few omissions of conventional endocrine disorders and a considerable portion of the modern laboratory researches have received notice. The work, however, to an endocrine specialist seems to lack unity. The book is attractively printed and will be a welcome addition to the physician's library.

The Thyroid and Its Diseases. Means, J. H., Pp. 602, J. B. Lippincott Company, Philadelphia, 1937.

The book is primarily "an account of the personal experiences of a considerable group of workers in a single thyroid clinic (that of the Massachusetts General Hospital) and of the opinions and convictions derived from this experience." It is, however, so well fortified by consideration of the pertinent literature as to amount, in effect, to an excellent general treatise.

The penetrating thoughtfulness and the delightfully original style of the author render the reading of the work both profitable and pleasant.

Traitié d'Endocrinologie (Les sécrétions internes au point de vue morphologique, chimique, physiologique, pathologique et thérapeutique) Les parathyroïdes. Parhon, C. I., and M. Goldstein, Pp. 524, Terek and Caminschi, Jassy, 1933.

The authors have long been known for their researches on the endocrine glands. They offer a review of current knowledge regarding the parathyroids, discussing them from both the laboratory research and the clinical points of view. Although the work runs to over 524 pages, it is printed on such thin paper as to make a compact volume. It should be highly useful to anyone wishing quickly to familiarize himself with the large subject treated.

The Eggs of Mammals. Pincus, Gregory, Pp. 160, The Macmillan Company, New York, 1936.

A concise and readable account is offered of the behavior of mammalian eggs from the time of their genesis to their implantation in the uterus. The influence of the follicular and pituitary gonadotropic hormones upon ovogenesis, growth, maturation and atresia is considered. The history of tubal ova is given with an account of the comparative behavior of fertilized eggs both in vivo and in vitro. The nature of parthenogenetic activation and fertilization as well as the intrinsic and extrinsic factors affecting cleavage are discussed. The development of the blastodermic vesicle is treated chiefly on the basis of the hormonal control of growth and implantation. Recently developed technics for obtaining and experimenting with mammalian ova are described. The book is attractively printed and illustrated with judiciously selected graphs and photographs. It closes with a good working bibliography.

Some Fundamental Aspects of the Cancer Problem. Symposium Sponsored by the Section on Medical Sciences of the American Association for the Advancement of Science. Edited by Henry Baldwin Ward, Pp. 248, The Science Press, New York, 1937.

This volume comprises a series of authoritative reviews brought together in a symposium in the American Association for the Advancement of Science (1936).

The articles of most interest to endocrinologists are those by Fieser, by Gardner, by Geschickter and Astwood, by Ferguson, and by Bagg. They deal with such topics as the relationship between carcinogenic action and sex hormones, relation of sex hormones to neoplastic formations, and teratoma testis. Those who are accustomed to think in simple terms of the relationship of hormones to oxidative processes and carbohydrate metabolism would do well to read Burk's discussion of various factors in biological oxidation; he reveals in a fascinating way some of the remarkably complex ramifications of the subject.

Endocrinology. Clinical Application and Treatment. Werner, August A., Pp. 672, Lea & Febiger, Philadelphia, 1937.

The strongest feature of this book is that it is by an experienced clinician writing on Endocrinology rather than vice-versa. It stems in considerable measure from the Engelbach school and as would be expected, emphasizes the practical point of view. In addition, however, the treatment throughout shows wide reading in the literature of modern research and no little skill in utilizing laboratory studies for the elucidation of clinical manifestations. There is a delightful freedom from a propensity to warp the evidence to bolster up preconceived theories or pet notions—a comment that cannot be made of some books written from a clinical orientation. While some readers will see in the book an undue confidence in present-day ability to differentiate anterior and posterior lobe pituitary disorders, the thesis stands on its own merits without being bolstered up by specious rationalization. Another evidence of broad-minded willingness to deal fairly with the subject is the refraining from knocking over the weather-beaten straw-man of "obeisance to the guinea-pig." In short, the author is neither over-impressed with, nor cavalier toward, laboratory findings.

The general scheme of the book is first to summarize current knowledge of anatomical, neurological, physiological and chemical foundation data. In so doing admirable judgment is shown in selection and without cluttering up the text with details or material incorporated merely to display erudition. He thus escapes the fallacies inherent in confusing the 'practical' with the *practical*. The greater part of the discourse is made up of discussions of clinical syndromes that arise from endocrine malfunctioning, taking up each endocrine gland, or system seriatim. In this section the book is weakest in its treatment of diabetes mellitus in that scarcely sufficient attention is paid to other glands than the pancreas as major factors. In a final section individual chapters on such topics as obesity, hair, and teeth are included.

The book is profusely illustrated throughout with photographs and case histories, largely original. In the treatment of endocrine therapy the author takes a medium position between that of the reluctant reactionary and that of the enthusiast.

The style is crisp and the text 'flows.' A few lapses from rhetorical elegance have escaped editorial attention but these are not obtrusive.

Altogether, the book is commended in high terms to anyone desiring a critical but hopeful introduction to the intricate and difficult subject of endocrinology.

Endocrinology in Modern Practice. Wolf, William, Pp. 1018, W. B. Saunders Company, Philadelphia, 1936.

This book presents a remarkably exhaustive compilation of data on clinical endocrinology. Much evidence from the experimental laboratories has also been included for its interpretative significance. The material is elaborately schematized in an attempt to afford an easy road to erudition. For each of the chief endocrine glands there are short sections on the anatomy, embryology, histology, biology and physiology, followed by an extensive clinical section.

The experienced physician who knows well the pitfalls and limitations of clinical endocrinology will find much of interest and value in the book. The less experienced clinician will encounter difficulties in his attempt to realize the promises, explicit or implicit, that are held out.

The book is well illustrated and attractively printed.

ADVANCE ABSTRACTS

Pituitary dwarfism with diabetes mellitus. Beck, H. G., and G. M. Suter. To appear in this Journal.

The case reported is that of a pituitary dwarf 17½ years of age, who developed diabetes at the age of 5 following scarlet fever. He was normal at birth and grew normally during early childhood. From the ages of 9 to 15 he grew only 4 in. on diabetic treatment, including insulin. During the ensuing 2½ years, when anterior pituitary therapy was added, he grew 8.37 in., and the genitalia developed normally. The paper is devoted to a discussion of the lack of correlation between clinical findings and experimental animal research.

The interrelation of pituitary and adrenal in the control of carbohydrate levels in the rat. Bennett, L. L. To appear in this Journal.

A comparison is made of the ability of crude anterior lobe extracts, adrenocorticotropic hormone, and adrenal cortical extracts to maintain fasting carbohydrate levels of hypophysectomized, hypophysectomized-adrenalectomized, and adrenalectomized rats. The administration to a 24-hour fasted hypophysectomized rat of 1 mg. of a crude anterior lobe extract per 100 gm. body weight maintains muscle glycogen at the normal level of approximately 500 mg.%; the muscle glycogen of untreated, fasted hypophysectomized rats is 320 mg.%. It requires 15 mg. per 100 gm. body weight of adrenocorticotropic hormone to produce a similar effect. The crude anterior lobe extracts maintain the muscle glycogen of fasted hypophysectomized-adrenalectomized rats at 480-545 mg. %. The extracts are given only during the fasting period to produce these effects. The muscle glycogen level of adrenalectomized rats showing adrenal insufficiency is 325 mg.%; this is restored by eschatin and salt therapy to 536 mg.% and 443% for unfasted and fasted rats respectively. The muscle glycogen of fasted hypophysectomized rats receiving the same therapy is 335 mg.%. Adrenalectomized rats do not develop inability to maintain muscle glycogen levels during fasting until the onset of other symptoms of adrenal insufficiency; hypophysectomized rats develop this defect immediately after operation. It is concluded that the pituitary directly, rather than through the mediation of the adrenal, influences the maintenance of carbohydrate levels in the fasting rat.

The effect of thyrotropic hormone, alone and with other substances, on the in vitro O_2 consumption of thyroid and liver. Canzanelli, A., and D. Rapport. To appear in this Journal.

After daily subcutaneous injections of thyrotropic hormone in guinea pigs for 5 or 6 days, the in vitro O_2 consumption of the thyroid is consistently elevated; that of the liver is sometimes, but not always, increased. When the thyrotropic hormone is incubated with guinea pig thyroid in vitro, a similar increased O_2 consumption is observed. When the hormone is incubated with liver, it has no such effect. When the hormone plus either thyroxin, thyroglobulin, or diiodotyrosin are incubated with either thyroid or liver, the effects produced are the additive ones of each of the test materials separately. From this it is concluded that the action of thyrotropic hormone on metabolism, through the thyroid, is not by virtue of a specific effect on either thyroxin, thyroglobulin, or diiodotyrosin. Thyrotropic hormone plus thyroid tissue, incubated for 4 hours with guinea pig liver, depressed the O_2 consumption of the liver, as did thyroid tissue alone. It is postulated that the thyroid may contain an inhibitory substance which normally checks the action of the thyroid hormone.

Keratodermia of the hands and feet and thyroid deficiency. Cervino, J. M., A. Bertolini and R. A. Larrosa Helguera. To appear in this Journal.

Two cases of thyroid deficiency are presented. The first is that of a 15-year-old girl with congenital hypothyroidism. The chief symptoms were adiposity, height under minimum normal for the age, mental retardation, menstrual disturbances characterized by profuse flowing with long intervals of amenorrhea, sensitiveness to cold, and constipation. The skin was thick, dry and harsh with marked hyperkeratosis of the palms of the hands and the soles of the feet. Thyroid substance was given in amounts varying between 0.10 and 0.20 gm. After a month of treatment the keratotic process in the palms and soles almost entirely disappeared. The second case was that of a woman with myxedema. Her skin was thick and dry and she also had marked hyperkeratosis of the palms and soles. She was placed on thyroid treatment until a dosage of 0.30 gm. daily was reached. There was marked improvement in the entire clinical picture.

The biological effects of thymus implantation in normal rats. Einhorn, N. H., and L. G. Rowntree. To appear in this Journal.

The administration of frequent homologous thymus implants in normal parent rats has resulted in a moderate accruing acceleration in the rate of growth and development in 4 successive generations of their offspring. This precocity is comparable to, although not as marked

as that resulting from the continuous intraperitoneal administration of 1 cc. of thymus extract daily in successive generations. The stimulation to growth and development provided by frequent thymus implantation is short in duration, lasting only as long as additional implants are made, and disappears rapidly after implantation is discontinued.

The biological effects of thymus implantation in thymectomized rats. Einhorn, N. H. To appear in this Journal.

The accruing retardation in growth and development incident to thymectomy in successive generations of rats has not only been completely corrected, but has been over-corrected by the utilization of frequent homologous whole gland thymus implants.

The biological effects of thymus extract (Hanson) on thymectomized rats. Einhorn, N. H. To appear in this Journal.

The accruing retardation in growth and development incident to thymectomy in successive generations of rats has not only been completely corrected but has been changed to a moderate accruing acceleration in growth and development by daily intraperitoneal injections of 1 cc. of thymus extract.

The diversified clinical and pathological pictures of failing ovarian function. Finkler, Rita S., and M. Friedman. To appear in this Journal.

A group of cases demonstrating diversified clinical pictures are presented. The underlying factor in these disturbances is considered to be that of failing ovarian function. This contention was verified not only by bio-assays, endometrial biopsies and histological studies of ovaries, but also by the response to therapy (estrin administration, or small dose x-ray therapy for stimulation purposes). The cases have been considered under the following sub-groups: uterine bleeding (excessive or diminished), compensatory pituitary hyperfunction, and adreno-genital syndrome. The unobscure clear-cut cases of primary and secondary amenorrhea are not included in this paper. Three cases of uterine bleeding and amenorrhea are presented, illustrating the fact that a failure of luteinization results at first in excessive bleeding. With the progression of the disturbance, there ensues a gradual diminution of estrin production and an amenorrhea. Compensatory pituitary hyperplasia is illustrated by a patient, age 28, subject to severe migraine headaches. Daily bio-assays over a period of one month showed an excessive excretion of the gonadotropic hormone and a corresponding diminished excretion of estrin. This pituitary hyperactivity was compensatory to the ovarian hypofunction. Intensive estrin and radiation therapy proved beneficial. The daily bio-assays after therapy showed a normal pituitary-ovarian relationship. The adreno-genital syndrome is illustrated by 2 cases, one of virilism, the other, pseudo-hermaphroditism. The ovarian hypofunction in both patients was apparently conditioned by an inhibitory influence originating in the adrenal gland. Unilateral adrenalectomy in one case and adrenal irradiation in the other have re-established menstrual periods.

Experimental development of the mammary gland of the monkey. Gardner, W. U., and G. van Wagenen. To appear in this Journal.

The mammary glands of male or ovariectomized immature female monkeys (Macacus rhesus) developed following the injection of estrogenic hormones (theelin, theelol and hydroxy-estrin benzoate). The glands first grew by a peripheral proliferation of the branching ducts. Lobules later developed, appearing first near the nipple. The experiments indicated that more than 22 weeks were required for the complete development of the glands, and growth was still in progress at 30 weeks. The nipples developed early in the experiments but showed little change in the later stages. Photographs and tables are given to show the extent and type of growth.

The relative effectiveness of emmenin, estriol glycuronide and estriol in the immature and the castrate immature rat. Greene, R. R., and A. C. Ivy. To appear in this Journal.

Sixteen castrate and 16 non-castrate immature rats were injected subcutaneously with emmenin. The average day of vaginal opening in the castrates was 6.06 days and in the non-castrate controls was 6.18. Two hundred and twenty-four castrate and the same number of non-castrate immature rats were given either emmenin, crystalline estriol glycuronide, or crystalline estriol. The response was determined by the vaginal smear method. One hundred or 49.01% of the castrates and 99 or 48.51% of the non-castrates showed a positive vaginal

response. It is concluded that emmenin, estriol glycuronide and estriol are not converted by ovarian tissue into a more potent form of estrogenic substance, and that estriol glycuronide and emmenin differ from estriol inasmuch as they are more potent by mouth than by subcutaneous administration.

The relation of the thyroid gland to the spontaneous activity of the rat. Hall, V. E., and Margaret Lindsay. To appear in this Journal.

In male rats, thyroidectomy produces a fall in spontaneous running in rotating cages to about one-half the preoperative level, this fall being completed within the first three days after the operation. The positive correlation between activity and basal metabolism, present in unoperated animals, persists after operation. Restoration of the normal resting metabolic rate by administration of dinitrophenol not only fails to restore normal activity but still further depresses the post-thyroidectomy level. The influence of the thyroid gland in maintaining normal activity of the type studied is therefore independent of its effect on the general bodily metabolic rate.

Quantitative cytological studies of the anterior lobe of the hypophysis of fetuses and children, correlated with sexual and skeletal development. Halpern, S. R. To appear in this Journal.

In 103 human fetuses and infants, the cells of the anterior lobe of the hypophysis were studied by counting with the oil immersion lens all the cells in every fifth field from three different levels of the gland. According to the size of the gland approximately 2,000 to 7,500 cells were counted in each case. The results obtained were statistically analyzed. The cases studied were divided into two groups, one comprising those under 55 cm. and the other over 55 cm. long. Fifty-five cm. represents the greatest length attained by any new-born in our series, while the cases above this length lived for varying lengths of time. In males and females under 55 cm. in length, the average percentage of each of the three cell types is as follows: males—chromophobes 59.1, acidophiles 22.8, and basophiles 18.0; females—chromophobes 58.1, acidophiles 26.6, and basophiles 15.8. In cases over 55 cm. in length, the results are as follows: males—chromophobes 43.6, acidophiles 37.5, and basophiles 17.5; females—chromophobes 48.2, acidophiles 38.2, and basophiles 14.6. Females have more acidophiles than males of a similar group. In the fetus and stillborn there are more chromophobes and basophiles, and less acidophiles than in the adult. A very definite correlation exists between length and weight and the number of acidophiles present. With an increase in length and weight there is a marked increase in the number of acidophiles, a slight increase in basophiles, and a decrease in chromophobes.

Effects of parathyroid extract and of vitamin D on blood phosphatase, calcium and phosphorus in osteogenesis imperfecta. Hansen, A. E., Irvine McQuarrie, and Mildred R. Ziegler. To appear in this Journal.

Parathyroid extract caused a marked decrease in the plasma phosphatase activity in 4 cases of osteogenesis imperfecta when given in doses of 20 U. daily for either 9 or 12 days. The serum calcium was increased and the inorganic phosphorus decreased. The total calcium and phosphorus balances became strongly negative following the administration of the extract. Very large doses of irradiated ergosterol given over periods of several weeks had similar effects. It is concluded that these substances only accentuate the disturbance in ossification already present and so are contraindicated as therapeutic agents.

Effect of cortin on the excretion of electrolytes. Hartman, F. A., Lena A. Lewis and C. Gwendoline Toby. To appear in this Journal.

The effect of intravenous injections (20-40 C.U.) of cortin on the renal excretion of electrolytes has been studied on 18 normal dogs. The initial response ranged as follows; sodium retention, 42-89%; chloride retention, 10-58%; pottassium for a 5% decrease to a 22% increase; the ammonia increase ranged from 23-110%. Electrolyte changes seem to be independent of urine volume. Urine pH did not change beyond the control range. Total base showed little change, the retention of sodium and the release of potassium and ammonia are always associated. Repeated injections in the same dog led to the development of a refractory state in which there was no response. This required several injections and several weeks for development. Four dogs, all that were tried, became refractory. The refractory state lasts for weeks, showing partial disappearance in 3 months. The refractory state can be transferred to a new dog by injection of serum from a refractory dog. The transferred refractory state seems

to be temporary. Similar results were obtained in the study of 6 normal human beings. The retention of sodium lasted for about 10 hours after a single intravenous injection of 5-50 C.U. of cortin. The refractory state also develops in the human being.

Some effects of adrenalectomy in fowls. Herrick, E. H., and Olaf Torstveit. To appear in this Journal.

The adrenal glands of young and mature male chickens were successfully removed by means of cautery. Adrenalectomized birds were maintained as long as 82 days by administering adrenal cortical extract, intermuscularly, and feeding large quantities of sodium chloride. Untreated birds died within a few hours after the operation. Following adrenalectomy the combs and wattles became pale in color and much reduced in size, resembling those of a capon. The testes likewise dwindled to only a fraction of their original size. The histological structure of the testes was altered, indicating marked degeneration.

The comparative efficacy of various androgens as determined by the rat assay method. Kochakian, C. S. To appear in this Journal.

The efficacy of various androgens was determined by the gravimetric rat assay method. The following order of increase in potency was found; androstanediol benzoate, androstenedione, testosterone oxime, testosterone benzoate, testosterone, urine extract, testosterone diacetate, testostrone acetate and testosterone propionate. Lengthening of the interval between injections resulted in a decrease in efficacy. The marked difference in the activity of the acetate, diacetate and propionate to the benzoate is attributed to the ability of the animal organism more satisfactorily to hydrolyse the former compounds. The relatively high potency of the urine extract is believed to be due to some factor or factors other than the known androgenic constituents. The weights of the adrenals of the rats used in this study were not affected.

Negative effects of endocrine extracts on the thymus of the white rat. Low, F. N. To appear in this Journal.

White rats were treated with endocrine extracts with the following results. Anterior pituitary extract (alpha and beta cell hormones) was injected daily. The results were negative. Ovarian residue extract (theelin) was injected daily. The results were negative. Desiccated thyroid substance was fed daily in non-toxic doses. The result was a 20% increase in the number of cortical lymphocytes. Eschatin (adrenal cortex extract) and parathyroid extract were injected daily. The results were negative. Various combinations of the foregoing extracts were injected daily. Negative results were achieved except in the cases of the animals treated with thyroid and ovarian substances. This treatment seemed to render the animals especially susceptible to respiratory disorders which caused involution of the thymus.

Further observations on the relation of the adrenal cortex to experimental diabetes. Lukens, F. D. W., and F. C. Dohan. To appear in this Journal.

Two adrenalectomized-depancreatized dogs, 2 depancreatized and partially adrenalectomized cats, and 2 hypophysectomized-depancreatized cats responded to the injections of large doses of adrenal cortical extracts with an increased severity of the diabetes. This response was determined by measuring the quantitative excretion of glucose, nitrogen and acetone bodies in the urine. The glucose and nitrogen excretion was approximately doubled and acetonuria appeared in 3 instances. Adrenalin did not appear to be related to this response. Certain conditions (salt intake, estrus, species, diuresis, etc.) which have been associated with the action of cortical extract are discussed in relation to the results.

The extraction of androgens from urine. McCullagh, D. R., and T. R. McLin. To appear in this Journal.

It is possible quantitatively to extract androgens from acidified boiled urine by stirring twice for 30 minutes with 20% by volume of dibutyl ether. Any emulsification which occurs can be controlled with sodium taurocholate. The extracts can rapidly be taken to dryness by steam distillation in vacuo with complete recovery of the solvent. Numerous bioassays have been performed to prove the validity of the method.

Clinical results of anterior pituitary therapy in children. A comparison of the value of oral and hypodermic preparations. M., Molitch, and S. Poliakoff. To appear in this Journal.

Thirty-two boys below the minimum in height for their age were divided into 3 groups and treated for 6 months as follows: group A received thyroid alone, group B received thyroid

plus anterior pituitary substance by mouth, group C received thyroid plus an anterior pituitary extract intramuscularly. Eleven additional boys were not treated but served as a control group. The 'treated' children had a greater increment in height than the control cases. The children who were already growing the most rapidly appeared to get the most stimulation. The outcome on all treated cases is so close that the results may be within the range of error.

Studies on fractions of the adrenal gland affecting sex organs. A maturation fraction administered orally possessing general male sex-stimulating properties especially promoting testicular descent. Pottenger, F. M., Jr., and D. G. Simonsen. To appear in this Journal.

The residue from the benzene fraction obtained by the Swingle and Pfiffner method of extracting adrenal glands contains a factor which is effective in restoring the physiologic balance of allergic children, and is gonadotropic. It may or may not be cortin. The fraction is a general maturating agent, affecting in no way normally developed individuals. The cases of 9 boys under treatment for asthma, presenting a concomitant failure of the descent of the testes, are presented. In from 3 month's to a year's treatment these 9 boys obtained complete descent of the testes. The case is also recorded of a mentally retarded 16-year-old boy whose genital development was that of a new-born baby. In 30 days' treatment the genital development had increased several times the original and the boy had made a marked advance in mental development.

Studies on fractions of the adrenal gland affecting sex organs. A male sex-stimulating, female sex-repressing hormone. Pottenger, F. M., Jr., and D. G. Simonsen. To appear in this Journal.

A new fraction of the adrenal gland has been tested experimentally on rats. The method of isolating the material in the form of an amorphous powder is described as well as the studies which have been made to ascertain where the fraction is found. The material, when administered to male rats, greatly increases spermatogenesis and the size of the testes. The same material given to female rats brings about a functional atrophy of the ovary and the lower genital tract.

Mineral metabolism of adrenalectomized rats studied by the appetite method. Richter, C. P., and J. F. Eckert. To appear in this Journal.

The mineral metabolism of adrenalectomized rats was studied by the appetite or self-selection method. Rats were given access to tap water and a number of different mineral solutions. In order to establish base lines records were taken for several weeks before the adrenalectomies were performed. Adrenalectomy produced an increase in appetite for sodium solutions other than sodium chloride. When access was provided simultaneously to sodium chloride, sodium phosphate, sodium iodide, calcium lactate, ammonium sulphate, potassium chloride and water, adrenalectomy produced an increase in appetite for the different ions which was fairly directly proportional to their distribution in normal blood serum, the intake being greatest for the sodium and chloride ions, smallest for the potassium and calcium ions, and about half way between for the lactate and phosphate ions. The ingestion of these different ions reduced the mortality to zero and produced normal growth and development. It was concluded that the adrenals regulate the metabolism of at least these six electrolytes contained in blood serum rather than only of sodium.

Changes in electrical potential during the oestrous cycle of the rat. II. Partial and complete hypophysectomy and pituitary replacement therapy. Rogers, P. V. To appear in this Journal.

It has been shown in a previous paper that the difference in electrical potential between the symphysis pubis and the vaginal canal varies, in the rat, according to the time in the oestrous cycle, and that the pattern thus formed is altered after ovariectomy. It has now been found that hypophysectomy has a similar effect on the normal type of potential. As in ovariectomized animals, the normal type of electrical potential curve may be reproduced in hypophysectomized rats by injecting threshold quantities of theelin. Hypophysectomized animals brought into oestrus with Prephysin show the characteristic rise in electrical potential only if luteinization occurs. Those rats whose pituitaries have been completely removed remain in oestrus indefinitely (all rats were killed after 8 days of oestrus), but when as little as 0.5% to 4% of pituitary is left, the follicles are luteinized and the normal rise in potential takes place.

The estimation of ovarian activity by the consecutive-day study of basal body temperatures and basal metabolic rates. Rubinstein, B. B. To appear in this Journal.

The B.M.R. of women of child-bearing age fluctuates during the menstrual cycle. The highest rate occurs about a week premenstrually; the lowest rate occurs just before the mid-period. The curve of B.M.R. variation parallels the curve of body temperature variation. High temperatures (99° F.-100° F.) and elevated B.M.R.'s during the premenstrual week may be normal, and should not be given much weight clinically unless the curve of either body temperature or B.M.R. is known in advance. The variation in body temperature and in B.M.R. offers a tool for the study of ovarian activity.

Treatment of genital hypoplasia in the male. Rubinstein, H. S. To appear in this Journal.

The treatment of genital hypoplasia in the male during the different age periods of the life cycle is discussed and a series of 8 illustrative case studies is reported. In infancy small doses of thyroid have been found usually to suffice for the production of testicular descent. In childhood and older states gonadotropic hormones have proved useful. These were either the water-soluble fraction of pregnancy urine, which was found most useful in patients with hypopituitarism, or the anterior-pituitary sex-hormones which is somewhat better in those patients whose pituitary functional defect is less striking. The water-soluble fraction of pregnancy urine increased the sex pace in one endocrinopathic patient. Early treatment is advisable to forestall skeletal disproportions and persistent hypoplasias. Since the accompanying personality difficulties may be quite distressing both the physical defects and the psychological maladaptations should receive appropriate and therapeutic attention.

The anterior pituitary factor which maintains muscle glycogen in fasted hypophysectomized rats. Russell, Jane A. To appear in this Journal.

The abnormal fall in body carbohydrate suffered by hypophysectomized rats during fasting was found to be prevented by the administration of extracts made from beef and sheep pituitaries. The muscle glycogen levels were principally affected, being restored to normal or above by treatment administered in divided doses over a period of 18 hours or more. It was necessary to start the treatment before or only shortly after the fasting period was begun. For assaying pituitary extracts for the substance termed the glycostatic factor which was responsible for the action described above, the minimum effective dose was defined as follows: when given to hypophysectomized rats in divided doses during a 24-hour fasting period, it maintained an average level of muscle glycogen of 450 mg.% in 3 to 5 animals. The M. E. D. was expressed in mg. per 100 gm. body weight and was proposed as a unit of glycostatic activity. From the quantitative comparison of several types of anterior pituitary extracts, it was concluded that glycostatic activity was not associated with the growth, adrenotropic, gonadotropic, lactogenic or thyrotropic hormones of the anterior lobe. The existence of a separate glycostatic factor, possibly but not certainly the same as that responsible for other metabolic effects of the anterior pituitary, was therefore postulated.

Calcium and phosphorus studies. The effect of repeated doses of parathyroid extract on the chemical composition of the blood and urine of the dog: an explanation of the cause of death in parathyroid overdosage. Shelling, D. H., L. Kajdi and Lenore Guth. To appear in this Journal.

The injection of frequent moderately large doses of parathyroid extract into dogs results in a profuse diuresis and a loss of water, sodium, chloride, calcium, and phosphorus from the body. After several hours of diuresis, however, the loss of water and electrolytes gradually diminishes, the loss eventually leading to oliguria, anuria, azotemia, and death. The ill-effects of parathyroid overdosage in dogs may be overcome by replacing the water and electrolytes lost by way of the kidneys. Glucose, although it may alleviate the symptoms of parathyroid poisoning in some cases by maintaining a urinary flow, can not be entirely relied upon to avert the fatal end-results, since it may accentuate the mineral loss. These experiments suggest that dehydration plays an important part in the production of the symptom-complex of parathyroid overdosage.

Study of the ratio of amount of theelin producing uterine and vaginal estrus. Szarka, A. J., and G. Kurtz. To appear in this Journal.

The amount of ketohydroxyestrin required to produce the characteristic uterine reaction of estrus in rats is 4.8 gamma. In the authors' colony and with the methods used, the uterine unit is 5 to 6 times the vaginal unit. The maximum uterine estrous reaction is reached 44 to

50 hours following the first injection, almost 24 hours sooner than the appearance in the vaginal smear of entirely non-nucleated cornified cells, characteristic of vaginal estrus. In the 72nd hour when the vaginal reaction is at its maximum, the uterine reaction has completely ceased. Considering the fact that the examination of the uterine reaction through laparotomies is simple, quick and dependable and entails but little loss in animals, it is suitable for the measurement of the potency of an unknown solution of estrin. It is not expected to replace the Allen-Doisy test, but, combined with it, the time required for the measurement is shortened. The biological effect of 4.8 gamma of crystalline ketohydroxyestrin seems to be equal to the effect of that quantity of hormone produced in the rat during the normal estrous cycle.

Further observations on the treatment of hypogenitalism and undescended testes, with special reference to the production of premature puberty. Thompson, W. O., N. J. Heckel, P. K. Thompson and L. F. N. Dickie. To appear in this Journal.

The anterior pituitary-like principle is valuable in the treatment of patients with undescended testes, both before and after surgical procedures. Before surgery, descent was produced in 8 of 36 undescended testes (22%) in 28 patients ranging in age from 1 to 37 years. If only the patients over 16 years of age are considered, then successful results were obtained in 32% of the cases. In patients showing no descent, stimulation of genital growth made subsequent surgical procedures less difficult. The material may be of value when previous attempts at surgical correction fail to bring the testes completely down, descent having been produced in 3 of 6 such instances. A striking feature of the administration of this material was the production of genital growth, which was occasionally so marked that premature puberty resulted. Only 2 of 33 patients with undescended testes were of the Fröhlich type. Ten of them had some congenital abnormality other than undescended testis. Because of its stimulation of genital growth, the anterior pituitary-like principle is valuable in the treatment of hypogenitalism, particularly of the Fröhlich type.

A study of the mechanism of edema associated with menstruation. Thorn, G. W., Katherine R. Nelson and Doris W. Thorn. To appear in this Journal.

The mechanism of edema associated with menstruation was investigated in the following manner. Normal male and female dogs were maintained on a constant food, fluid and mineral intake. The animals were kept in metabolism cages and catheterized at the termination of each 24-hour period. Crystalline preparations of several of the sex hormones were injected and the effect on the 24-hour renal excretion of electrolytes was observed. All of the sex hormones tested appeared to produce a temporary retention of sodium, chloride and water. Estradiol and progesterone were found to be the most active in this respect. Changes which occur in the body weight of normal women during the menstrual cycle were studied in a group of 50 nurses and dietitians. More complete metabolic and hormonal studies were made on 4 normal women and on 2 patients known to have a marked disturbance in body weight during the menstrual cycle. In these studies the subjects were maintained on a constant diet and a constant fluid and mineral intake. The 24-hour renal excretion of electrolytes was observed throughout one complete menstrual cycle. Estrone and pregnandiol determinations were made throughout the menstrual cycle on pooled 72-hour urine specimens. The time of ovulation was determined by the subsequent appearance of pregnandiol (degradation product of progesterone) in the urine. A gain in body weight (1 kg. or more) was observed in 24 of 50 normal women during the premenstrual period. An increase in appetite and thirst was a striking symptom observed during this period. However, a significant gain in body weight was also noted during the intermenstrual period (ovulation?) in 38 of 50 normal women. Experimental and clinical observations indicate that the sex hormones induce sodium, chloride and water retention. The cyclical increase in the secretion of the sex hormones and an increase in appetite and thirst appear to be important factors in the production of weight increase during the menstrual cycle.

ADRENALS

Studies on the mechanism of morphine hyperglycemia. The rôle of the adrenal glands. Bodo, R. C., F. W. CoTui and A. E. Benaglia, J. Pharmacol. & Exper. Therap. **61**: 48. 1937.

Normal dogs receiving 10 mg. morphine per kg. and normal cats receiving 8 mg. per kg., show a hyperglycemia which is usually noticeable in 15 minutes. The hyperglycemia becomes marked in 45 minutes and reaches a maximum within 2 hours. The standard time for

comparison was taken at 105 minutes after injection. The right adrenal was removed and the left, denervated and demedullated. The same dosage of morphine injected into the operated animals showed only a very slight hyperglycemia or none at all.—E. L.

Survival of rats after double adrenalectomy. Treatment with sodium chloride and with cortin. (Conditions de survie du rat après surrénalectomie double. Traitement par le chlorure de sodium et traitement par la cortine). Boilot, Y., A. Choay and A. Demolis, Compt. rend. Soc. de biol. **123:** 1074. 1936.

In 250 rats, males survived the operation 7½ days and females 6½ days, on the average. Twenty-five carefully selected castrated males averaged 8 days. If salt solution was injected subcutaneously, the survival period could be raised to an average of 17½ days, while with cortin the animals lived until the treatment was stopped.—J. C. D.

Experimental and clinical studies on adrenal insufficiency. Cleghorn, R. A., E. W. McHenry, G. A. McVicar and D. W. Overend, Canad. M. A. J. **37:** 48. 1937.

The assay of adrenal cortical extract on adrenalectomized dogs requires careful control of diet; even so, dogs may vary by 300% in their requirements per kg. for maintenance. Cats require approximately 10 times as much extract per kg. as dogs. The extract is useful in Addison's disease, especially in crisis; a case which could not be maintained on salt alone is described.—D. L. T.

Adrenal cortex extract in canine anaphylactic shock. Dragstedt, C. A., M. A. Mills and F. B. Mead, J. Pharmacol. & Exper. Therap. **59:** 359. 1937.

Eighteen dogs, sensitized with horse-serum, were injected with adrenal cortex extract. Test-doses of horse serum produced typical anaphylactic shock reactions, but the severity was less in the animals receiving extract. The resistance of the animals receiving cortical extract evidently was increased as the amounts of histamine liberated in the blood stream of the treated and untreated animals were the same.—E. L.

Suprarenal cortex therapy in the vomiting of pregnancy. Freeman, W., J. M. Melick and D. K. McClusky, Am. J. Obst. & Gynec. **33:** 618. 1937.

The 78 cases treated were divided into 4 grades of severity, and to the milder types the cortex extract was given orally: for the more severe types hypodermic injections were followed by oral therapy after relief was underway. The preparation was the Armour extract, the dose equivalent to 3 grains of dried gland t. i. d. The results were strikingly successful, none of the severe cases (31) having to be interrupted. All cases had been treated with conventional methods previously without relief. No contraindications to therapy were recognized. No data are given to judge of adrenal functional deficiency save mention of a striking and almost uniform weakness of the patients.—E. L. S.

Investigation of the carbohydrate metabolism of guinea pigs (Untersuchungen über den Kohlenhydratstoffwechsel des Meerschweinchens). Gottdenker, F., Biochem. Ztschr. **281:** 128. 1935.

Guinea pigs were subjected to a fast of 16 hr. and then blood samples drawn during 8 hr. at 2-hr. intervals. In late fall a blood sugar rise of 250% and more was found, even if the animals were fed during the 8-hr. period. In winter this hyper-glucemic condition was not found in the same animals. After a 16-hr. fast 2 gm. glucose per kg. body weight, administered by stomach tube, produced alimentary hyperglucemia, the first maximum being reached after 30 to 60 minutes. During the following 2 to 5 hr. the blood sugar curve passed through a minimum in some cases below the fasting level and finally increased beyond the first maximum. Subcutaneous injection of 0.2 cc. adrenalin hydrochloride (1:1000 of various sources) per kg. body weight produced after 2 to 3 hr. a rise in blood sugar of 250 to 500%. The further part of the blood sugar curve remains to be ascertained. In a great majority of animals after a 16-hr. fast, injection of 2 U of insulin per kg. body weight caused severe hyperglucemic convulsions without marked decrease in the blood sugar level. Some animals showed no blood sugar decrease while in others even hyperglucemia occurred. By fermentation experiments with yeast it was demonstrated that the high blood sugar values were not caused by an increase of non-sugar type reducing substances. It was concluded that in the guinea pig lack of blood sugar can not be the sole cause of these convulsions.—F. Breuer.

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ORIGINAL ARTICLES

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●

BEGINNING January 1938, ENDOCRINOLOGY will be published monthly, instead of bimonthly as heretofore.

This change was recommended by the Council and voted by the Association at the annual meeting in Atlantic City, June 8, 1937.

Two volumes, of about 700 pages each, will be issued annually. The general appearance, style and content of the Journal will remain much as at present. An important addition will be the inclusion each year of a series of authoritative editorial review articles by various active workers, dealing with recent progress in and the current status of various branches of endocrinology. Both clinical and experimental aspects will be reviewed.

The subscription price of the Journal will be changed to $10 per year, for two volumes.

The prompt publication of a greater amount of original research in endocrinology and the inclusion of informative review articles will make the Journal more valuable to subscribers than ever before.

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ENDOCRINOLOGY, the official publication of The Association for the Study of Internal Secretions, comprises original articles, case reports, occasional editorial articles, news items, book reviews and abstracts of current literature in experimental and clinical endocrine biology and medicine.

Original articles are accepted for publication only with the understanding that they are contributed *exclusively to this journal.* Preliminary notices will not be accepted.

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